# The Total Synthesis of Depsilairdin

A Thesis

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University of Saskatchewan

Saskatoon

By

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॥ Shree Ganeshay Namah ॥
॥ Shree Kalikay Namah ॥
॥ Om Namah Shivay ॥

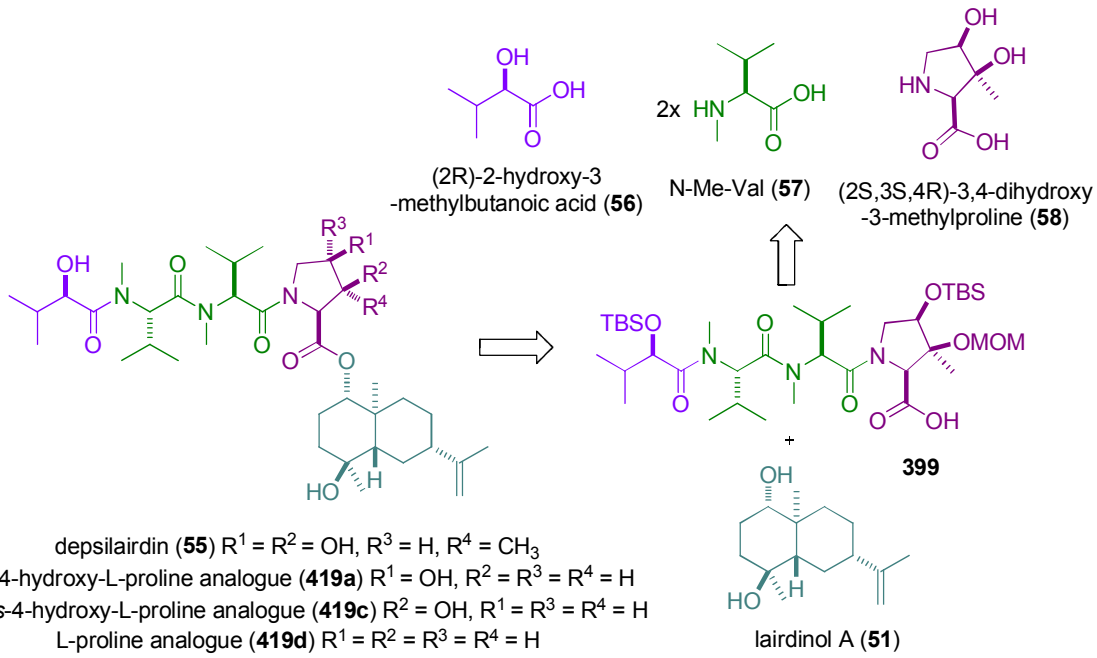
***Dedicated to my parents,***

***Govindsing Pardeshi and Sumitrabai Pardeshi.***

***It is because of them that, I am what I am.***

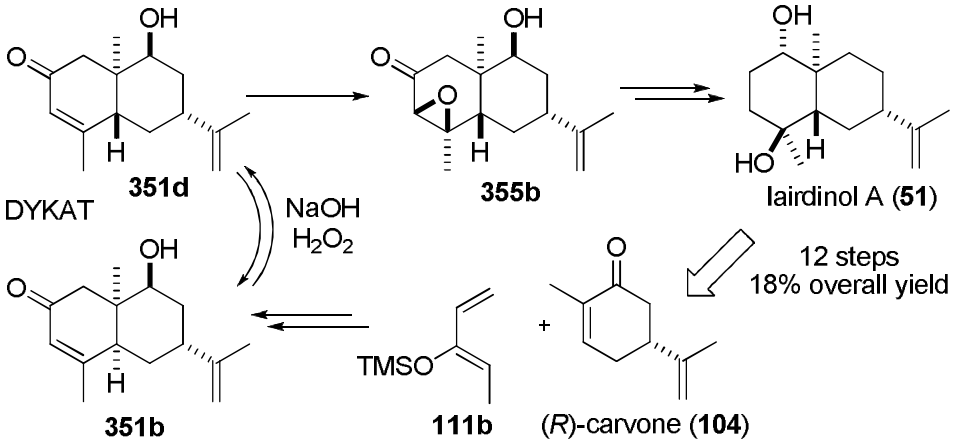
# Abstract

The acyclic depsipeptide depsilairdin is a host-selective phytotoxin obtained from the fungus *Leptosphaeria maculans* (Desm.) Cs. et de Not., asexual stage *Phoma lingam* (Tode ex. Fr.) and *L. biglobosa*, the causative agent of blackleg disease (Blackleg disease has caused heavy losses of canola and other economically important cruciferous oilseed plant in Canada and worldwide). The phytotoxin depsilairdin was found to be highly selective towards brown mustard leaves, forming strong necrotic and chlorotic lesions, while canola and white mustard leaves were unaffected. Depsilairdin (**55**) consists of five residues; (2*R*)-2-hydroxy-3-methylbutanoic acid (**56**), two *N*-methyl-L-valine (*N*-Me-Val) (**57**), a novel proline [(2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline] (**58**) and a sesquiterpene fragment, lairdinol A. Efficient total syntheses of depsilairdin (**55**) and its L-proline, *cis*-4-hydroxy-L-proline and *trans*-4-hydroxy-L-proline analogues are described.



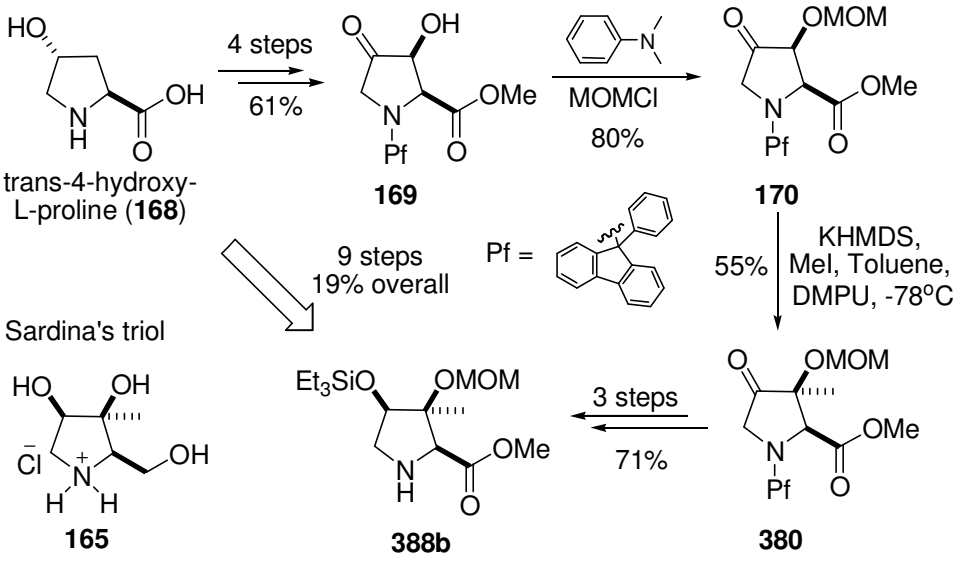
For the purpose of the total synthesis of **55**, it was necessary to synthesize the fragments in concise way. The syntheses of (2*R*)-2-hydroxy-3-methylbutanoic acid (**56**) and *N*-methyl-L-valine (*N*-Me-Val) (**57**) are known from D-valine and L-valine, respectively, however syntheses of [(2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline] (**58**) and lairdinol A (**51**) have not been previously reported.

The synthesis of lairdinol A was successfully achieved in 12 steps (18% overall yield) without the use of protecting groups starting with the Diels-Alder reaction of (*R*)-carvone with 3-trimethylsilyloxy-1,3-pentadiene. The key step established the trans ring fusion via (type III) dynamic kinetic asymmetric transformation (DYKAT) involving preferential epoxidation of a trans-fused enone in an equilibrating mixture of the cis-fused and trans-fused diastereomers. The synthesis confirmed the absolute configurations of lairdinol A and its enantiomer, cyperusol C.



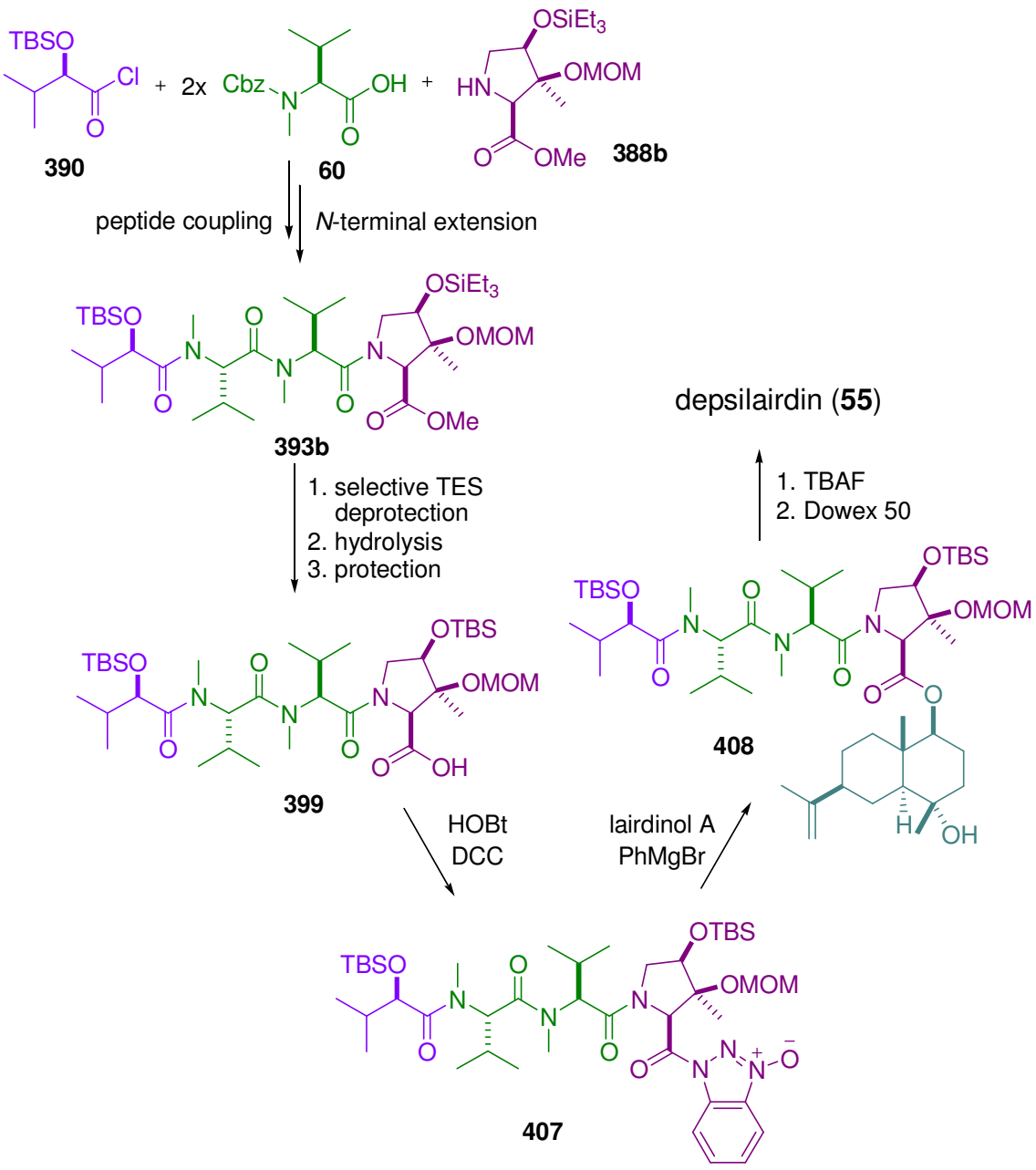

The synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline was achieved by adapting Sardina's synthesis of a structurally related triol (**165**). Despite the previous report, extensive optimizations were required to reproduce the MOM protection of the

hydroxy-ketone and the alkylation of the corresponding ketone. The synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline was ultimately achieved in 9 steps with 19% overall yield from *trans*-4-hydroxy-*L*-proline.




During the synthesis of depsilairdin (**55**) the desired tetrapeptide fragment **399** was built up by using the *N*-terminal extension strategy (*C*←*N*) for peptide synthesis. The tetrapeptide methyl ester is quite sterically hindered and its hydrolysis could not be achieved under a variety of conditions that were attempted (e. g. LiOH, $Me_3SnOH$, KOTMS, etc.). Thus, the success of the synthesis relied on an intramolecularly assisted, $Me_3SnOH$ mediated hydrolysis of a differentially protected tetrapeptide methyl ester where the $2^o$ alcohol group in the proline moiety was unprotected. Esterification of the resulting acid with lairdinol A was also one of the most challenging steps and was achieved via the corresponding HOBt (1-hydroxybenzotriazole) activated ester of **407**. Treatment of **407** with the putative bromomagnesium alkoxide prepared by reaction of

lairdinol A with PhMgBr gave the desired depsipeptide which upon deprotection afforded depsilairdin (**55**).




The hydrolyses of the tetrapeptide methyl esters in the analogues **416a**, **416c** and **416d** were much more facile than **398b** and could be achieved directly with $Me_3SnOH$ and LiOH without any modifications in the tetrapeptide fragment. Coupling of the

resulting tetrapeptide acids with lairdinol A was achieved in good yields using DCC/DMAP. However, the hydrolysis of the tetrapeptide moiety in compound **416b** was also difficult but could be achieved via corresponding diol using $Me_3SnOH$.

These are the first reported syntheses of the natural products lairdinol A (**51**) and depsilairdin (**55**). The key steps in the synthesis of depsilairdin were *N*-terminal extension (*C*←*N*) of the protected proline fragment, hydrolysis of the tetrapeptide fragment with free $2^o$ alcohol in the proline moiety and esterification of the HOBt ester of tetrapeptide fragment with the bromomagnesium alkoxide of lairdinol A (**51**).

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# List of abbreviations

| | |
|---|---|
| α | observed optical rotation in degrees |
| $[\alpha]_D$ | specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are implied) |
| Å | angstrom |
| Ac | acetyl |
| AD | asymmetric dihydroxylation |
| AIBN | azobisisobutyronitrile |
| anhy | anhydrous |
| AOP | (7-azabenzotriazol-1-yl)oxytris(dimethylamino) phosphonium hexafluorophosphate |
| ap | apparent (spectral) |
| aq | aqueous |
| Ar | aryl |
| atm | atmosphere(s) |
| BDDC | bis[4-(2,2-dimethyl-1-3dioxolyl)]methylcarbodiimde |
| Bn | benzyl |
| Boc | *t*-butyloxycarbonyl |
| BOP | benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate |
| BOP-Cl | *N*,*N*'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride |
| br | broad (spectral) |
| BRSM | based on recovered starting material |

| | |
|---|---|
| Bu, *n*-Bu | normal (primary) butyl |
| *t*-Bu | *tert*-butyl |
| °C | degrees Celsius |
| cal | calorie(s) |
| Cbz | carbobenzyloxy |
| CI | chemical ionization; configuration interaction |
| CIP | 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate |
| $cm^{-1}$ | wave number(s) |
| cod | 1,5-cyclooctadienyl |
| concd | concentrated |
| COSY | correlation spectroscopy |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| Cy | cyclohexyl |
| δ | chemical shift in parts per million downfield from tetramethylsilane |
| d | day(s); doublet (spectral); deci |
| DA | Diels-Alder |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N,N'*-Dicycohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEPC | diethylphosphonocyanidate |
| DEPT | distortionless enhancement by polarization transfer |
| DET | diethyl tartrate |

| | |
|---|---|
| DIPA | *N*,*N*-diisopropylamine |
| DIPEA | *N*,*N*-diisoproylethylamine |
| dil | dilute |
| DKP | diketopiperazine |
| DMA | *N*,*N*-dimethylaniline |
| DMAP | 4-(*N*,*N*-dimethylamino)pyridine |
| DME | 1,2-dimethoxyethane |
| DMF | dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (*N*,*N*'-dimethylpropyleneurea) |
| DMSO | dimethyl sulfoxide |
| DPTC | *O*,*O*'-di(2-pyridyl)thiocarbonate |
| dr | diastereomeric ratio |
| DRIFT | diffuse reflectance infrared Fourier transform spectroscopy |
| DYKAT | dynamic kinetic asymmetric transformation |
| EDCI·HCl | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimde hydrochloride |
| ee | enatiomeric excess |
| *ent* | Enantiomer of |
| equiv | equivalents |
| ESI | electrospray ionization |
| Et | ethyl |
| EVK | ethyl vinyl ketone |

| | |
|---|---|
| FAB | fast atom bombardment |
| FCC | flash column chromatography |
| FDDP | pentafluorophenyl diphenyl phosphate |
| Fmoc | 9-fluorenylmethyl carbamate |
| g | gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g., gCOSY, gHSQC) |
| GC | gas chromatography |
| h | hour(s) |
| HAMDU | *O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate |
| HAPyU | 1-(1-pyrrolidinyl-1H-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate-*N*-oxide |
| HATU | *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetra- methyluronium hexafluorophosphate |
| HBTU | *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HLF | Hofmann-Loffler-Freytag |
| HMBC | heteronuclear multiple bond correlation |
| HMPA | hexamethylphosphoric triamide (hexamethylphosphoramide) |
| HOAt | 1-hydroxy-7-azabenzotriazole |
| HOBt | 1-hydroxybenzotriazole |
| HONSu | *N*-hydroxysuccinimide |
| HPLC | high performance liquid chromatography |

| | |
|---|---|
| HRMS | high-resolution mass spectrometry |
| HSQC | heteronuclear single quantum correlation |
| Hz | Hertz |
| IR | infrared |
| IPCC | isopropenyl chlorocarbonate |
| *J* | coupling constant (in NMR spectrometry) |
| k | kilo |
| K | Kelvin(s) (absolute temperature) |
| *K*eq | equilibrium constant |
| L | liter(s) |
| LDA | lithium diisopropylamide |
| LTA | L-threonine aldolase |
| HMDS | hexamethyldisilazane, bis(trimethylsilyl)amide |
| lit. | literature |
| LRMS | low-resolution mass spectrometry |
| $\mu$ | micro |
| m | multiplet (spectral); meter(s); milli |
| M | molar (moles per liter); mega |
| $M^+$ | parent molecular ion |
| max | maximum |
| Me | methyl |
| MED | methyl ethyl dioxolane |
| MHz | megahertz |

| | |
|---|---|
| min | minute(s); minimum |
| mM | millimolar (millimoles per liter) |
| mol | mole(s); molecular (as in mol wt) |
| MOM | methoxymethyl |
| MoOPH | oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric-triamide) |
| MS | mass spectrometry; molecular sieves |
| MVK | methyl vinyl ketone |
| MW, mol wt | molecular weight |
| *m/z* | mass-to-charge ratio |
| N | normal (equivalents per liter) |
| NBS | N-bromosuccinimide |
| NDC | nicotinium dichromate |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| PCC | pyridinium chlorochromate |
| PDC | puridinium dichromate |
| Pf | 9-phenylfluoren-9-yl |
| Ph | phenyl |
| PMA | phosphomolybdic acid |
| ppm | part(s) per million |
| PPTS | pyridinium-*p*-toluenesulfonate |

| | |
|---|---|
| Pr | propyl |
| $^{i}$Pr | *iso*-propyl |
| Pro | proline |
| PTLC | preparative thin layer chromatography |
| PTSA | *p*-toluenesulfonic acid |
| PyBOP | benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate |
| PyBroP | bromotri(pyrrolidino)phosphonium hexafluorophosphate |
| PyCloP | chlorotri(pyrrolidino)phosphonium hexafluorophosphate |
| py | pyridine |
| q | quartet (spectral) |
| rt | room temperature |
| s | singlet (spectral); second(s) |
| t | triplet (spectral) |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBAI | tetra-*n*-butylammonium iodide |
| TBDMS, TBS | *t*-butyldimethylsilyl |
| TBHP | *t*-butyl hydroperoxide |
| TES | triethylsilyl; triethylsilane |
| Tf | trifluoromethanesulfonyl (triflyl) |
| TFA | trifluoroacetic acid |
| TFDO | Methyl(trifluoromethyl)dioxirane |
| TFFH | tetramethylfluoroformamidinium hexafluorophosphate |

| | |
|---|---|
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| TMEDA | *N,N,N′,N′*-tetramethyl-1,2-ethylenediamine |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TMS | trimethylsilyl; tetramethylsilane |
| TOF | time-of-flight |
| Ts | tosyl |
| UV | ultraviolet |
| Val | valine |
| vol | volume |
| v/v | volume per unit volume (volume-to-volume ratio) |
| WSCI | water soluble carbodiimide; i.e., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| wt | weight |
| w/w | weight per unit weight (weight-to-weight ratio) |

# 1 Introduction

## 1.1 Blackleg disease

Blackleg, a fungal disease of cruciferous oilseed plants, is caused by at least two known fungal species; *Leptosphaeria maculans* (Desm.) Ces. et de Not., asexual stage *Phoma lingam* (Tode ex. Fr.), highly virulent on canola, and *L. biglobosa* (low virulence on canola). It has caused heavy losses of canola (*Brassica napus* L. and *B. rapa*) and rapeseed (*B. napus* and *B. rapa*) in Canada and worldwide. The loss of cruciferous oilseed plants due to blackleg disease has been known for over a century and was first reported in Saskatchewan in 1975 and also found in every canola growing region of the country. Yield losses of up to 50 percent have been reported for severely infected fields.[1, 2]

The blackleg pathogen can survive for several years in infected seeds. When infected seeds are planted, seedlings emerge and develop infectious cotyledon, leaves and stems. Infections from seeds can result in early and widespread epidemics and can cause dramatic losses. Seed transportations from infected areas to other regions have contributed to the widespread epidemic of blackleg disease throughout the world. Ideally, the spread of blackleg disease from an infected seed to the seedling can be prevented by seed treatment; however this does not protect the seedlings from getting infected by airborne spores. When leaves are infected, the fungus can move into the plant's vascular tissue to the stem base. Stem lesions girdle the stem base by preventing the flow of water up to the stem and often result in lodging of crops. Pod infections can

also result in infected seeds that serve as another source of inoculums for future infestation.[1]

A number of methods are available to control the severity and spread of blackleg disease. Crop rotation is an effective way to defeat the blackleg disease; it allows time for the diseased plant residues to decompose and thus remove the inoculum source. Sanitation, burning or burying the infected crop residues also help in controlling the disease to a great extent. Modern methods such as development of blackleg resistant species are among the most promising ways to control the disease. Chemical treatment of seeds with fungicides before sowing also protects the emerging seedlings from infections. Despite these preventive measures, a more effective disease control method is still required.[1, 2] Numerous researches are being carried out by scientists in an effort to understand the chemistry of plant-pathogen interactions. For instance, analysis and characterization of isolated metabolites from plants that were put under chemical, physiological or biological stresses could yield important clues to help design new environmentally benign chemical measures to protect plants.

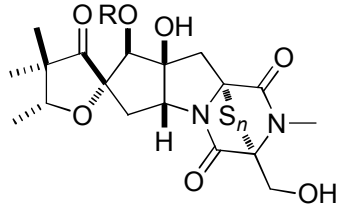
### 1.1.1 Secondary metabolites from *Leptosphaeria maculans*

Metabolic processes in living organisms synthesize and degrade a variety of chemical compounds. Primary metabolism comprises those parts of the metabolic processes that occur in all living organisms and produces primary metabolites such as phytosterols, lipids, nucleotides, amino acids, and organic acids. In addition to primary metabolism, other metabolic pathways occur in living organisms that involve the production of secondary metabolites (e.g. terpenoids, alkaloids, fatty acids, peptides etc.).[3]

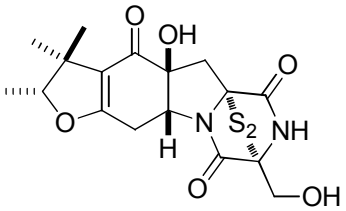
Phytotoxins are secondary metabolites produced by fungal or bacterial plant pathogens that are harmful to plants; however, for many the modes of action and bioactivities are unknown. The secondary metabolites produced by the blackleg fungus have been studied in an effort to understand and control the disease. A wide variety of structures, such as dioxopiperazines, polyketides, sesquiterpenes, and depsipeptides having diverse biological activities have been isolated from the fungal cultures of *L. maculans* and are briefly reviewed below.

### 1.1.1.1 Dioxopiperazines and related metabolites from *Leptosphaeria maculans*

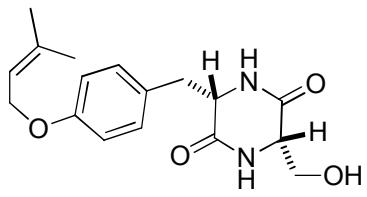
Blackleg fungal cultures are a rich source of metabolites and an array of metabolites has been isolated from them. Several different dioxopiperazines were isola-



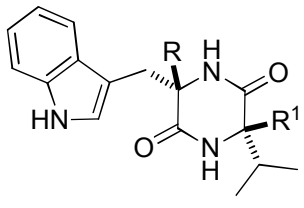
R = Ac *n* = 2 sirodesmin PL (**1**)
R = H *n* = 2 deacetylsirodesmin PL (**2**)
R = Ac *n* = 1 sirodesmin H (**3**)
R = Ac *n* = 3 sirodesmin J (**4**)
R = Ac *n* = 4 sirodesmin K (**5**)



phomalirazine (**6**)



phomamide (**7**)



R = $R^1$ = H polanrazine A (**8**)
R = $R^1$ = SMe polanrazine B (**9**)
R = OH; $R^1$ = SMe polanrazine C (**10**)
R = SMe; $R^1$ = OH polanrazine D (**11**)
R = OH; $R^1$ = OMe polanrazine E (**12**)
R = $R^1$ = OH polanrazine F (**13**)

**Figure 1.1**. Dioxopiperazines isolated from *Leptosphaeria maculans*.

-ted from fungal extracts of cultures of *L. maculans* (Figure 1.1). Sirodesmin PL (**1**) and deacetylsirodesmine PL (**2**) represented a new class of phytotoxins and were isolated from the blackleg fungus by Ferezou *et al.* in 1977.[4] Pedras and co-workers isolated sirodesmin H (**3**) in 1988[5] and sirodesmins J and K (**4**, **5**) in 1990[6] from the fungal cultures of *L. maculans.* The structures of these dioxopiperazines were determined by traditional spectroscopic techniques.

Phomalirazine (**6**) was isolated in 1989[7] and its structure was elucidated using spectroscopic data and later was confirmed by X-ray crystallography. Phomalirazine was reported to be a biosynthetic intermediate between sirodesmins and phomamide. A biosynthetic pathway was proposed for sirodesmins that involved the transformation of phomamide (**7**) into sirodesmine PL **1** via phomalirazine (**6**).

Polanrazine A (**8**) also known as L-valyl-L-tryptophan anhydride was disclosed by Pedras *et al.* in 1998[8] while polanrazines B-F (**9**-**13**) were isolated in 2001 from the fungal cultures of *L. maculans* virulent to brown mustard.[9] Phytotoxicity studies of polanrazines A-E carried out on blackleg susceptible and resistant plants showed that polanrazines C (**10**) and E (**12**) caused necrotic and chlorotic lesions on brown mustard leaves at a concentration of $5 \times 10^{-4}$ M while canola and white mustard leaves remained unaffected at this concentration.[9]

Recently, several new metabolites were described during a search for plant stress inducing metabolites from *L. maculans* (Figure 1.2). Isolation and characterization of these metabolites e.g. leptomaculins A-E (**14**-**22**) have been reported.[10] All the leptomaculins are structurally related to sirodesmins (**1**-**5**, Figure 1.1). To date, leptomaculins A (**14**) and B (**15**) are the only examples of 2,3-oxopiperazinethione and

2,3-dioxopiperazine respectively isolated from Nature. The structures of **14** and other leptomaculins were determined by spectroscopic techniques and the structure of **14** was also confirmed by X-ray analysis. Phytotoxicity studies revealed that leptomaculins A-E are non-toxic to *B. juncea* and *B. napus*.

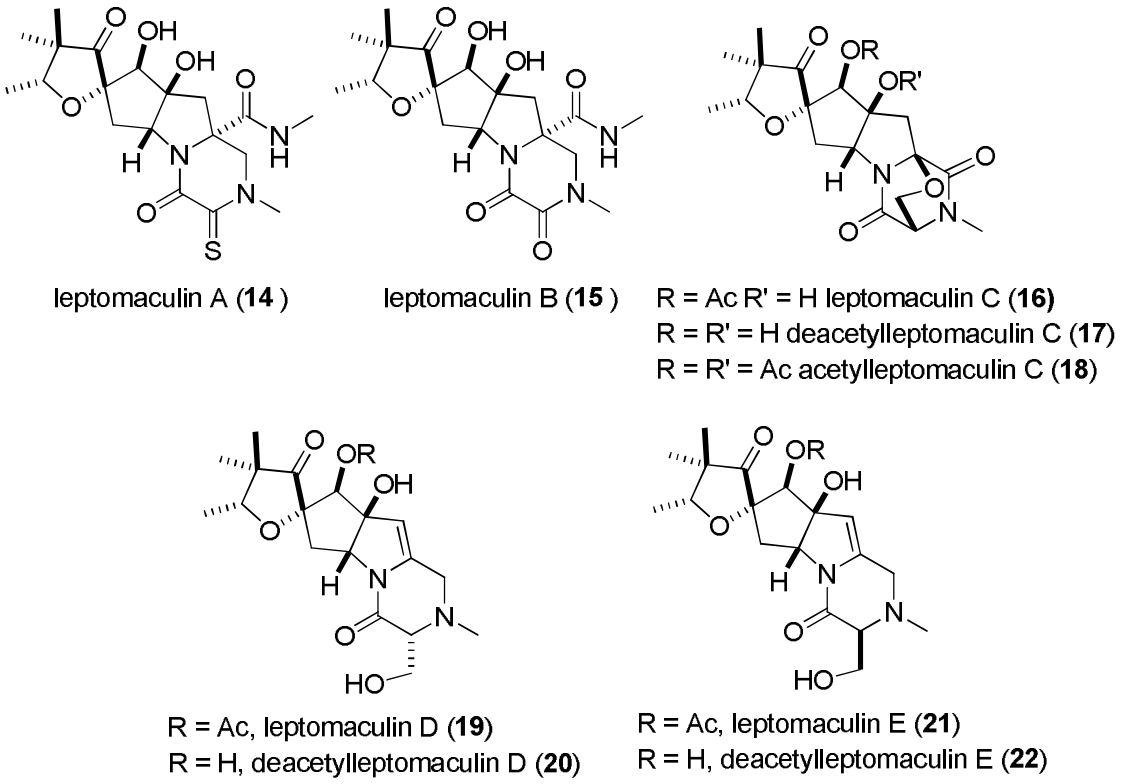
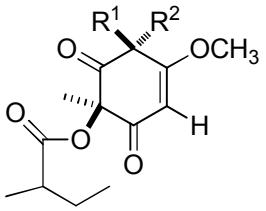


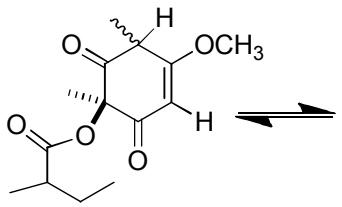

**Figure 1.2**. Leptomaculins isolated from *Leptosphaeria maculans*.

### 1.1.1.2 Polyketides from *Leptosphaeria maculans*

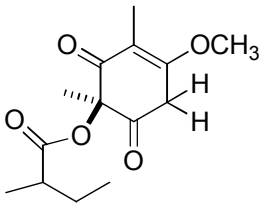
Several ploykетide derived phytotoxins were isolated from *L. maculans* (Figure 1.3). Phomaligols A (**23**), $A_1$ (**24**), phomaligadiones A (**27/28**) and B (**29**) were reported in 1993.[11] Compounds **27/28** and **29** are in equilibrium with each other via tautomerism. The hydroperoxides of phomaligols (**25** and **26**) were reported by Pedras *et al.*[12] Toxicity studies suggested that phomaligols A and B are non-toxic to blackleg susceptible canola



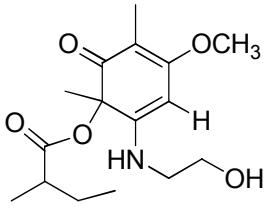
$R^1 = CH_3$; $R^2$ = OH phomaligol A (**23**)
$R^1$ = OH; $R^2 = CH_3$ phomaligol $A_1$ (**24**)
$R^1 = CH_3$; $R^2$ = OOH
hydroperoxide of phomaligol A (**25**)
$R^1$ = OOH; $R^2 = CH_3$
hydroperoxide of phomaligol $A_1$ (**26**)



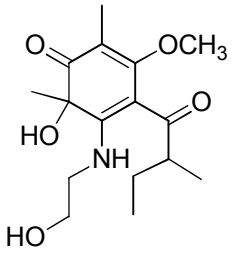
phomaligadiones A (**27/28**)



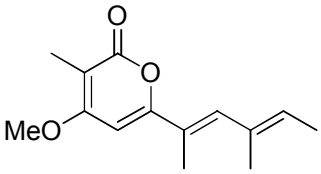
phomaligadione B (**29**)



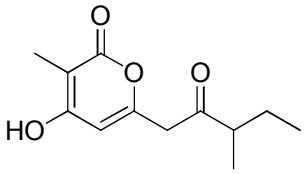
wasabidienone E (**30**)



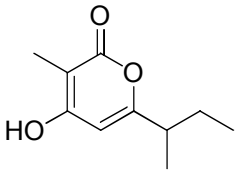
phomaligin A (**31**)



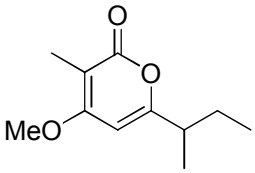
phomapyrone A (**32**)



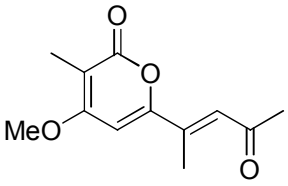
phomapyrone B (**33**)



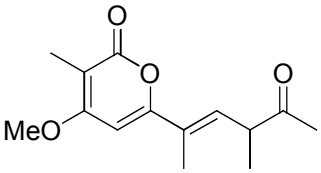
phomapyrone C (**34**)



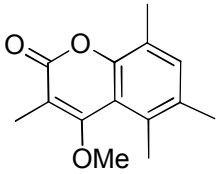
methyl phomapyrone C (**35**)



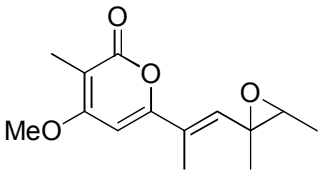
phomapyrone D (**36**)



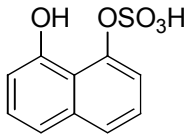
phomapyrone E (**37**)



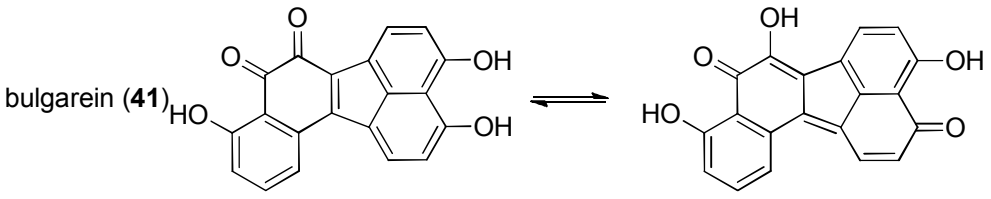
phomapyrone F (**38**)



phomapyrone G (**39**)



8-hydroxynaphthalene-1-sulfate (**40**)



bulgarein (**41**)

**Figure 1.3**. Polyketides isolated from *Leptosphaeria maculans*.

species even at a relatively high concentration ($10^{-3}$ M) while wasabidione E (**30**) and phomaligin A (**31**) caused only slight lesions at a concentration of $10^{-3}$ M.[12]

Phomapyrones A, B, C (**32**-**34**), methyl phomapyrone C (**35**)[13] and phomapyrones D-G (**36**-**39**) were reported by Pedras *et al.*[14] Phytotoxicity assays on phomapyrones showed that phomapyrones A (**32**) and D (**36**) had no activity even at a concentration of $10^{-3}$ M.

A new metabolite, 8-hydroxynaphthalene-1-sulfate (**40**) has been isolated from the fungal cultures of *L. maculans* grown under high salt concentration.[15] The chemical structure of **40** was elucidated by using spectroscopic data and was later proven by synthesis starting from 1,8-dihydroxynaphthalene. The fungal metabolite bulgarein (**41**, present in equilibrium with its enol form) was also isolated from the same culture. Bulgarein was previously isolated by Edwards *et al.* from the fungus *Bulgaria inquinans* in 1976.[16, 17] A complete characterization of **41** was reported recently by Pedras and co-workers. Both compounds **40** and **41** showed no phytotoxic activity.[15]

#### 1.1.1.3 Sesquiterpenic phytotoxins from *Leptosphaeria maculans*

Several sesquiterpenic phytotoxins were also isolated from the fungal cultures of *L. maculans* (Figure 1.4). Phomalairdenone A (**42**) was isolated in 1999 from the blackleg fungal cultures, Mayfair 2 and Laird 2.[18] It was found that **42** caused lesions on *B. juncea* while *B. napus* remained unaffected at the same concentration. Other sesquiterpenic phytotoxins such as phomalairdenones B-D (**43**-**45**), phomalairdenols A-D (**46**-**49**), selin-11-ene-4α-ol (**50**) and lairdinol A (**51**) were also isolated from the same fungal culture.[19] Selin-11-ene-4α-ol (**50**) was previously isolated from *Podocarus dacrydioides* by Corbett *et al.*[20]

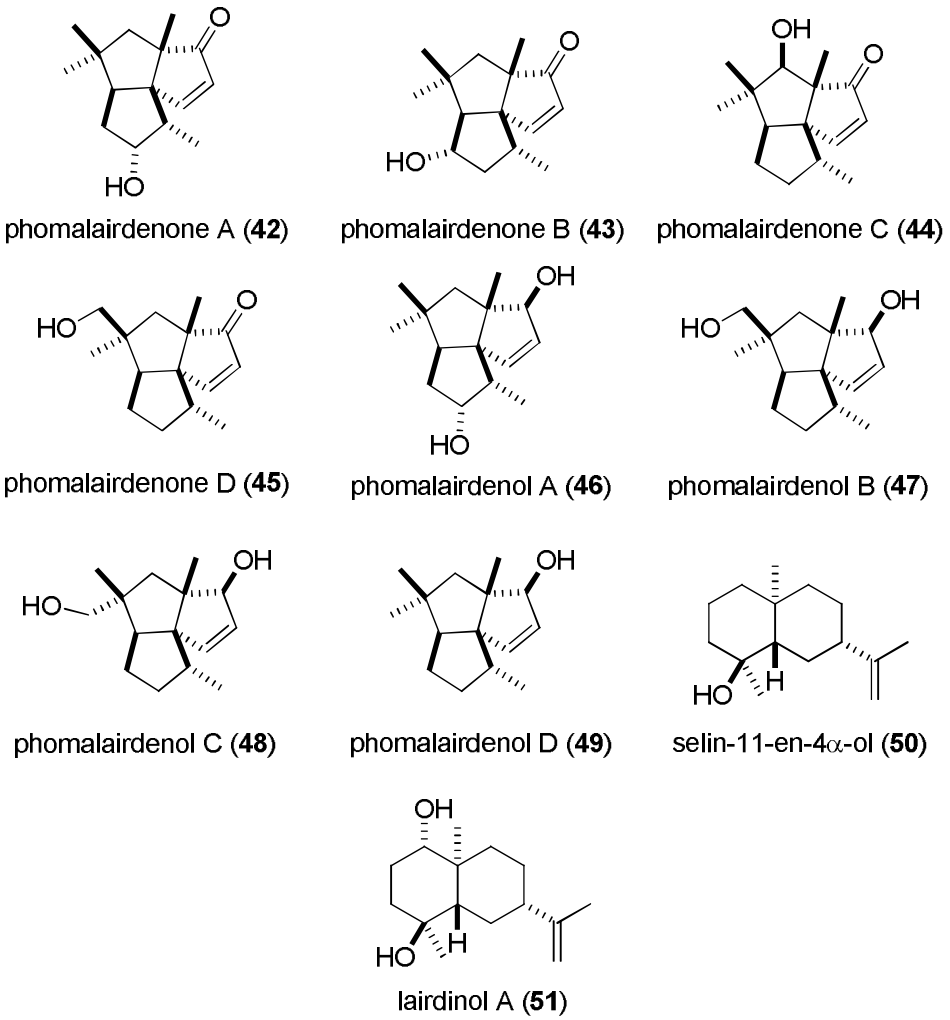



**Figure 1.4**. Sesquiterpenic metabolites from *Leptosphaeria maculans*.

The structures of these sesquiterpenes were deduced by spectroscopic methods. Phytotoxicity assays showed that phomalairdenone D, phomalairdenols A-C and lairdinol A were toxic to *B. juncea* only whereas no toxicity was observed in *B. napus*.[19]

### 1.1.1.4 Host-selective phytotoxins from *Leptosphaeria maculans*

Phytotoxins which are harmful only to the host plant and relatively harmless to non-host plants are known as host-selective phytotoxins. Several host-selective phytotoxins have been isolated from the fungus *L. maculans* (Figure 1.5). Pedras and co-workers have recently disclosed two new phytotoxins, maculansins A (**52**) and B (**53**). The structure of **52** was determined by using spectroscopic methods and chemical degradation. The backbone of **52** was found to be *D*-mannitol, which was determined after hydrolysis of **52** followed by acetylation of the degraded product. It was observed that maculansin A (**52**) is very selective towards resistant *B. juncea* (brown mustard) and harmless to susceptible species of canola (*B. napus*) and white mustard (*Sinapis alba*) at a concentration of 0.1 mM while at increased concentration (1 mM) all three species showed similar damage. Compound **52** diffuses in the leaf tissue and causes the irregular leaf lesions which are similar to those caused by the pathogen and host-selective phytotoxin depsilairdin (**55**, *vide infra*).[21]

Depsipeptides have also been isolated from the fungal cultures of *L. maculans*. Phomalide (**54**), which was disclosed in 1993,[22] is a cyclic depsipeptide that contains residues of L-valine (Val), D-leucine (D-Leu), (2*S*)-2-hydroxy-4-methylpentanoic acid (Hmp), (2*S*)-2-hydroxy-3-phenylpropanoic acid (Hpp) and (*E*)-2-amino-2-butenoic acid (Aba). The three-dimensional structure of **54** was determined by chemical degradation and spectroscopic methods. The chemical synthesis of phomalide (**54**) by Ward *et al.* confirmed the previous structural assignment of **54**.[23, 24] Phytotoxicity studies of phomalide showed that it causes lesions on blackleg susceptible canola species similar to that caused by the blackleg disease. However, blackleg resistant *B. juncea* was

unaffected even at relatively higher concentrations which makes phomalide a host-selective phytotoxin.[22]

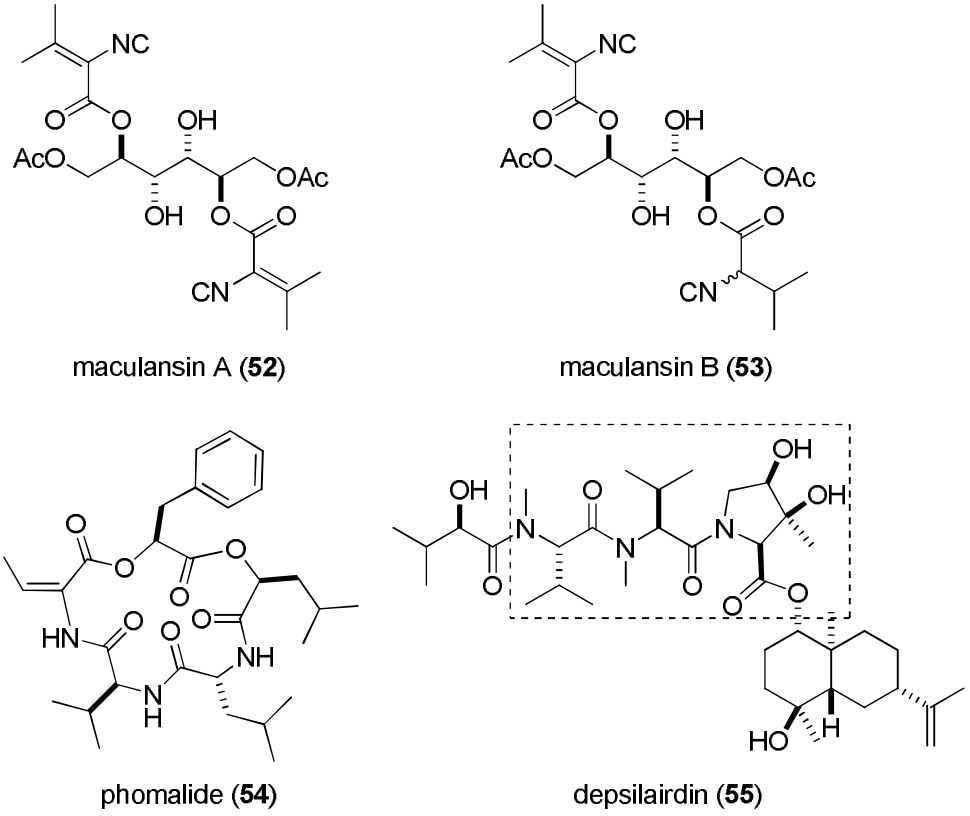



**Figure 1.5**. Host-selective phytotoxins from *Leptosphaeria maculans*.

A new host-selective phytotoxin, depsilairdin (**55**), was recently isolated by Pedras *et al.* from the fungal cultures of *L. maculans* virulent to brown mustard.[25] Depsilairdin (**55**) is an acyclic depsipeptide (compounds containing ester as well as amide linkages) which contains residues of (2*R*)-2-hydroxy-3-methylbutanoic acid (Hmb, **56**), *N*-methyl-L-valine (*N*-Me-Val, **57**), a novel proline [(2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline, **58**], and a sesquiterpene fragment lairdinol A (**51**) (Figure 1.6). Depsilairdin is highly selective towards brown mustard leaves forming strong necrotic and chlorotic lesions while canola and white mustard leaves were unaffected.[25]

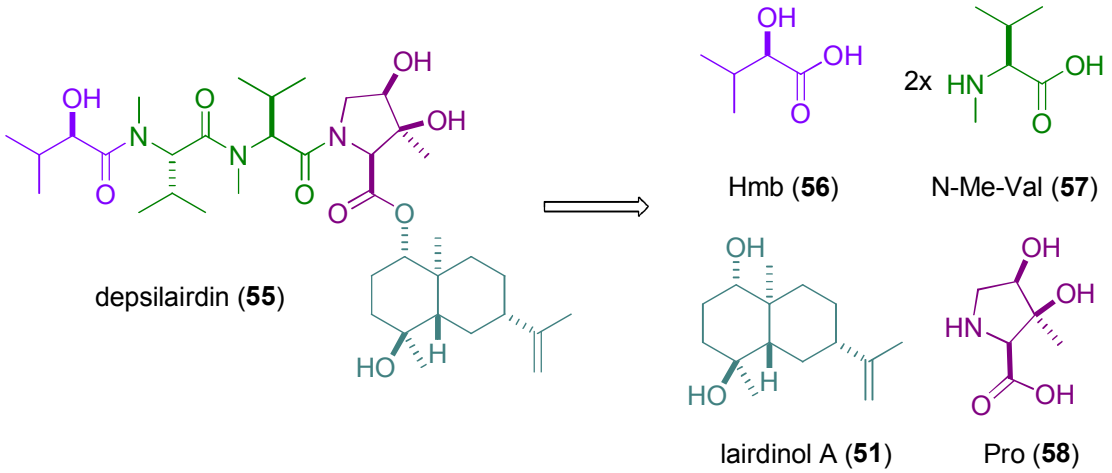



**Figure 1.6**. Four major components of depsilairdin.

A list of the metabolites isolated from cultures of *L. maculans* of different virulence is shown in Table 1.1.

**Table 1.1**. Metabolites from *Leptosphaeria maculans* and *L. biglobosa* virulent to canola and brown mustard.

| **Metabolite From *L. maculans*** | **Virulent to canola (*B. napus*)** | **Virulent to brown mustard (*B. juncea*)** |
|---|---|---|
| Polanrazine C | No | Yes |
| Polanrazine E | No | Yes |
| Phomalairdenone A | No | Yes |
| Phomalairdenone D | No | Yes |
| Phomalairdenol A | No | Yes |
| Phomalairdenol B | No | Yes |
| Phomalairdenol C | No | Yes |
| Lairdinol A | No | Yes |
| Maculansin A | Yes | Yes |
| Phomalide | Yes | No |
| Depsilairdin | No | Yes |

## 1.2 Structure determination of depsilairdin by Pedras and co-workers[24]

The structure elucidation of depsilairdin was accomplished using the modern techniques and chemical degradation methods. The molecular formula $C_{38}H_{65}N_3O_9$ was determined by HRMS and other spectroscopic data such as 1-D and 2-D NMR of **55** showed the presence of eight degrees of unsaturation. $^1$H NMR of **55** showed six methyl singlets and six methyl doublets, $^{13}$C NMR showed the presence of four carbon signals between $\delta_C$ 170-175 ppm representing the ester or the amide carbonyls and signals at $\delta_C$ 108.4 and 150.1 strongly indicated the presence of a double bond. The presence of three rings deduced from NMR data accounted for the remaining three sites of unsaturation.

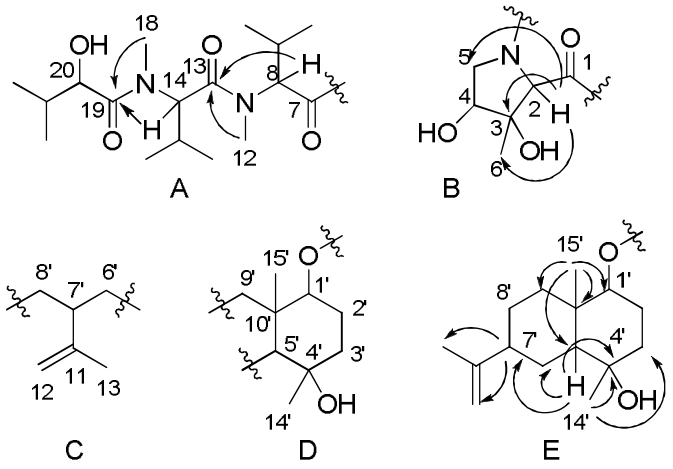


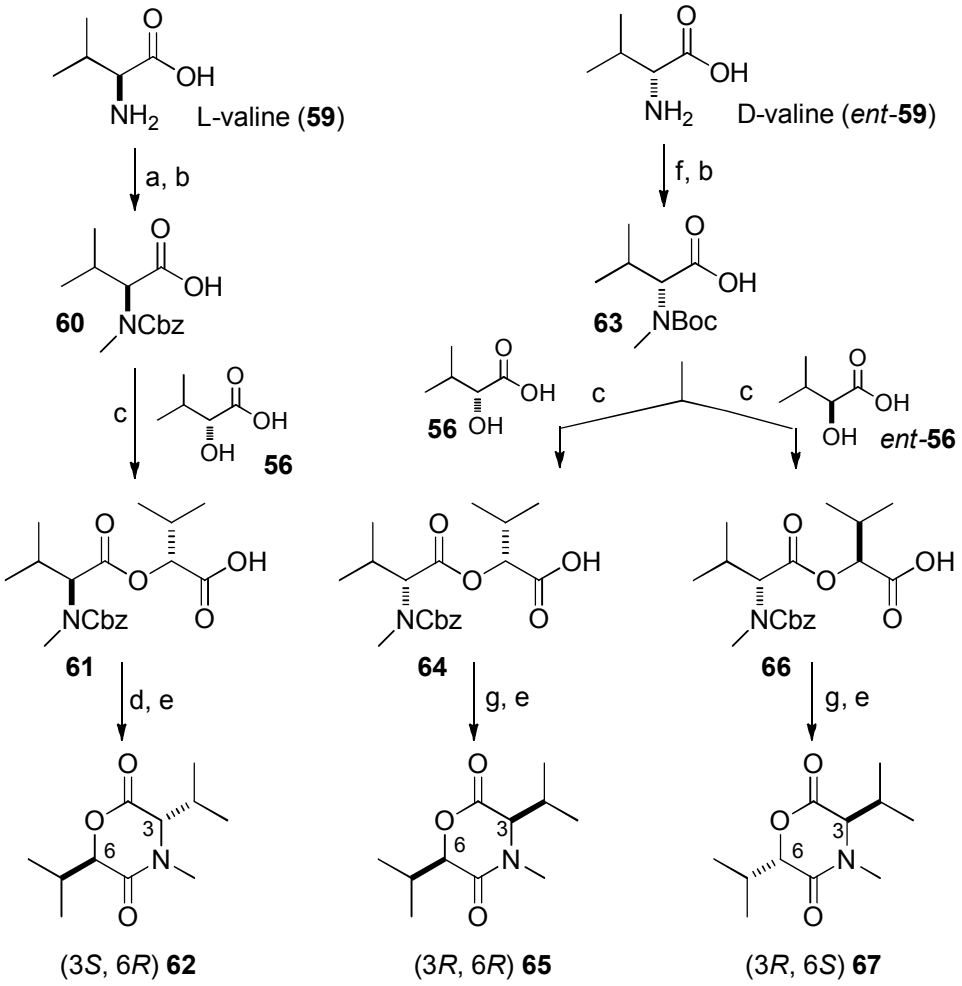

**Figure 1.7**. Selected HMBC correlations.

Two dimensional COSY analysis indicated the presence of part structures A-E and selected HMBC correlations are shown in Figure 1.7. The methine proton signals at $\delta_H$ 5.34 (H-14, d, $J$ = 11 Hz), 5.29 (H-8, d, $J$ = 11 Hz) and 4.22 (H-20, d, $J$ = 7 Hz) showed HMBC correlation as indicated in part structure A. HMBC correlation were observed as

shown in part structure B for proton at $\delta_H$ 3.68 which was coupled with protons at $\delta_H$ 4.48 and 3.89 (m, 2xHC-5) (Figure 1.7). Other spin systems were identified via COSY and HMBC are shown in part structures C, D and E. The connectivity between the part structure B and E was revealed from HMBC correlation of proton at $\delta_H$ 4.89 (H-1', dd, *J* = 12, 4 Hz) of substructure E and the carbonyl carbon at $\delta_C$ 171.1 (C-1) of substructure B. Depsilairdin was crystallized from acetone-hexane (7:3) and its relative configuration was confirmed by X-ray analysis.[25]

To determine the absolute configuration, depsilairdin was chemically degraded to trans-3,6-diisopropyl-4-methyl-2,5-morpholinedione by treatment with DCl and $CD_3OD$. Three different 3,6-diisopropyl-4-methyl-2,5-morpholinediones were synthesized to determine the absolute configuration in the degraded product (Scheme 1.1). $^1$H NMR spectra of **62** and **67** matched with the degradation product while that of **65** was significantly different. To confirm which enantiomer was identical with the degradation product, $^1$H NMR of **62**, **67** and the degradation product were obtained in the presence of (*R*)-(⁻)-TFAE as the chiral solvating agent. $^1$H NMR analysis showed that the degradation product was identical to (3*S*,6*R*)-3,6-diisopropyl-2,5-morpholinedione (**62**).[25]

**Scheme 1.1**. Syntheses of 3,6-diisopropyl-4-methyl-2,5-morpholinediones.



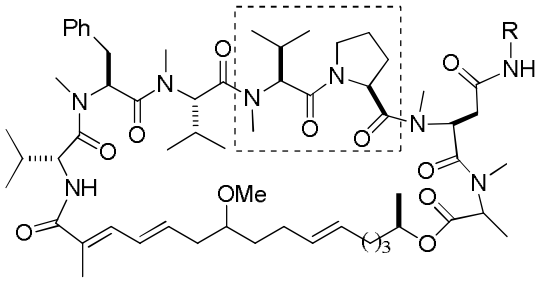

**Reagents and Conditions:** (a) CbzCl, NaOH, $H_2O$; (b) NaH, MeI, THF; (c) CDI, THF; (d) $H_2$, Pd/C; (e) $Et_3N$, 2-chloro-1-methylpyridinium iodide; (f) $(Boc)_2O$, NaOH, dioxane; (g) $HCO_2H$ excess.

Depsilairdin was found to have highly selective toxicity towards brown mustard causing strong necrotic and chlorotic lesions while other mustard plants such as white mustard and canola remained unaffected even at a relatively higher concentration ($10^{-3}$M). The phytotoxicity of **55** mimics the pathogen as it causes symptoms in brown mustard similar to those caused by the fungus.[25]

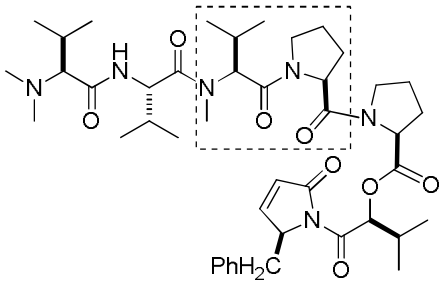
Depsilairdin was considered to be a synthetically interesting target with respect to its biological properties and its challenging architecture. The aim of this research was to develop an efficient synthetic route to depsilairdin with the potential to provide useful amounts for biological evaluations. Depsilairdin consists of five residues coupled together as shown in Figure 1.6. The major issues to address during the synthesis are, (a) the synthesis of the sesquiterpene moiety lairdinol A (**51**), (b) the synthesis of the novel proline fragment (**58**) and, (c) the coupling of the five fragments. In the next few sections, brief summaries of literature precedents describing the construction of similar sesquiterpene fragments, syntheses of related proline derivatives and finally methods/tactics used to couple sterically bulky fragments by esterification and amide bond formation in natural product synthesis will be discussed.

### 1.2.1 Natural products containing *N*-Methyl-valyl-proline peptide linkages

Depsilairdin (**55**) has an interesting *N*-Me-valyl-proline peptide linkage, a common structural motif found in numerous natural products having interesting biological activities, some of them are illustrated below.



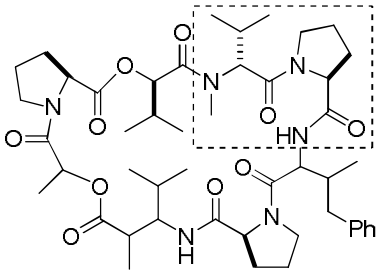
Dolastatin 14 R = H (**68**)
Malevamide E R = $CH_3$ (**69**)



Dolastatin 15 (**70**)

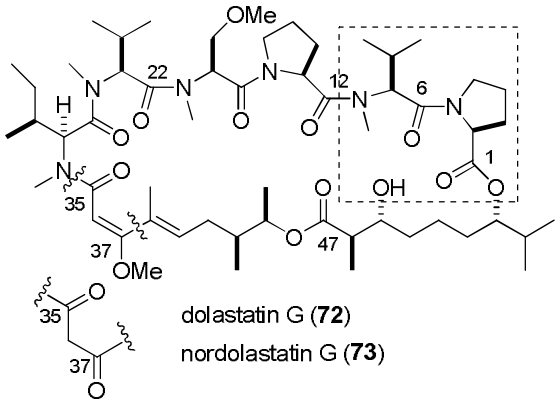
Dolastatin 14 (**68**) was isolated by Pettit from *Dolabella auricularia.* Active against NCI murine P388 lymphocytic leukemia ($ED_{50}$ 0.022 pg/mL).[27] Malevamide E (**69**) Horgen *et al.* from Cyanobacterium *Sympoca laete-Vividis.* Showed dose dependent (2-45 µm) inhibition of store-operated $Ca^{2+}$ entry in thapsigargin-treated human embryonic kidney (HEK) cells[28]

Dolastatin 15 (**70**)[26] isolated by Pettit from *D. auricularia* $ED_{50}$ = 2.4 ng/mL



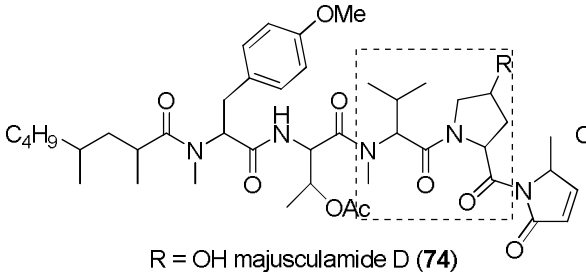
Dolastatin 16 (**71**)

Dolastatin 16 (**71**)[29] was isolated by Pettit from *D. auricularia.* $GI_{50}$ values of $2.5x10^{-7}$ M against Human cancer cell lines.



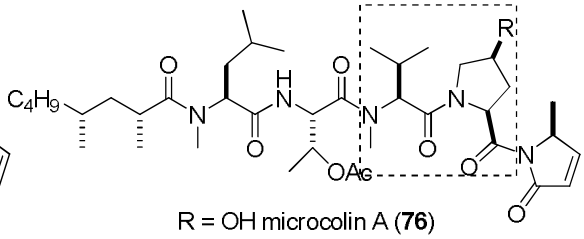
dolastatin G (**72**)
nordolastatin G (**73**)

Dolastatin G (**72**) and nordolastatin G (**73**) were isolated by Yamada[30] from *D. auricularia* Active against HeLa S3 (IC50 of 1.0 and 5.3 µg/mL respectively) cell lines.



R = OH majusculamide D (**74**)
R = H deoxymajusculamide D (**75**)

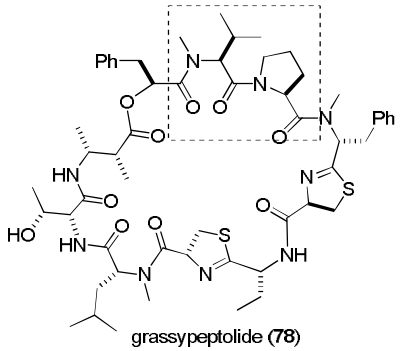
Isolated from *Lyngbya majuscula*. Active towards CCRF-CEM cell lines.[31]



R = OH microcolin A (**76**)
R = H microcolin B (**77**)

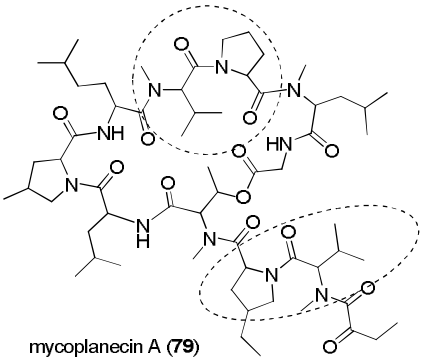
Isolated by Koehn from *L. majuscula.* against murine P388 leukemia with an $IC_{50}$ of 0.4 µg/ml.[32]

**Figure 1.8**. Examples of natural products containing *N*-Me-Val-Pro linkage.



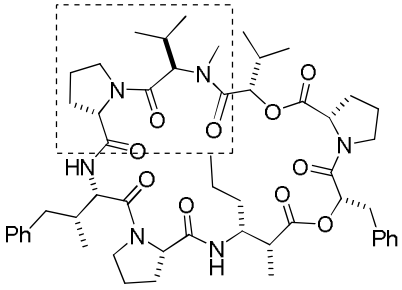
grassypeptolide (**78**)

Isolated from *L. confervoides*
Active against various cell lines such as human osteosarcoma, cervical carcinoma ($IC_{50}$ values from 1.0 to 4.2 $\mu$M).[33]



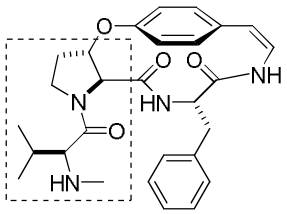
mycoplanecin A (**79**)

Isolated from *Actinoplanes awajinensis* subsp. mycoplanecinus subsp. Nov. Active against *M. intracellulare.* Minimal inhibitory concentration (1.5-0.1 $\mu$g/mL) [34-36]



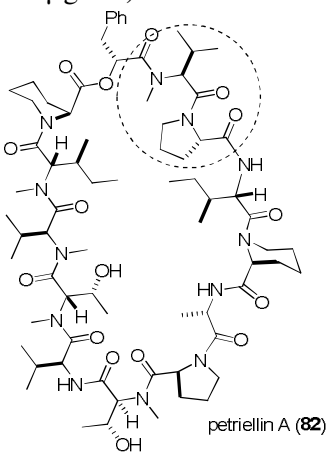
kulokekahilide-1 (**80**)

Isolated from *Philinopsis speciosa*.
Active against P388 murine leukemia cells ($IC_{50}$ = 2.1 µg/mL).[37]



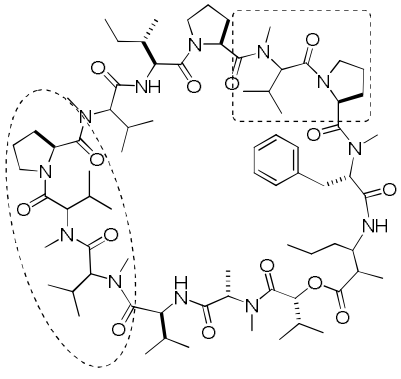
mauritine C (**81**)

Isolated from *Zizyphus mauritania Lam.* active against the Gram-positive bacteria *Bacillus subtilis*. [38]



petriellin A (**82**)

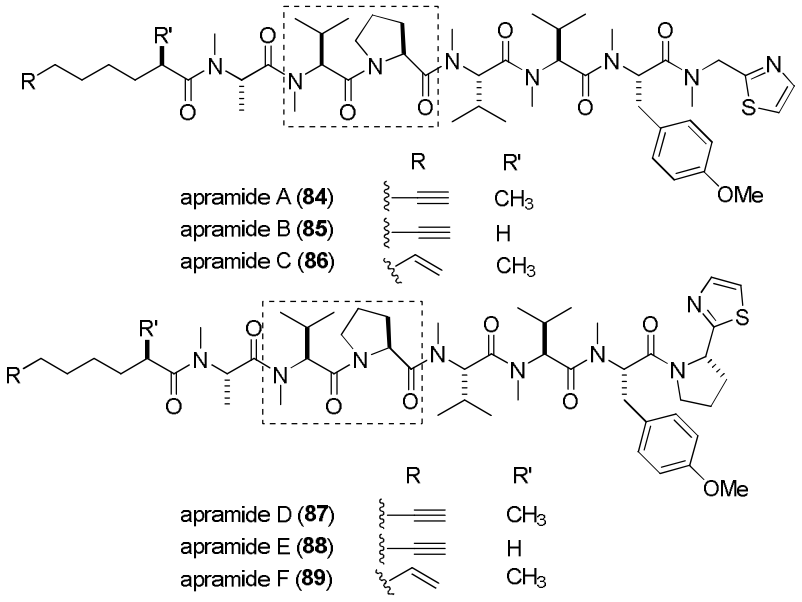
Isolated from *Petriella Sordida*
Active against fungi *Ascobolus furfuraceus* and *Sordaria fimicola*, with minimal inhibitory concentration 5 pg/mL and 52 pg/mL, respectively.[40]



malevamide B (**83**)

Isolated from *Symploca laete-viridis*
Not active against several cell lines.[39]

**Figure 1.9**. Examples of natural products containing *N*-Me-Val-Pro linkage.




Apramides A-F (**84**-**89**) were isolated by Luesch *et al.* in 2000 from *L. majuscula* and were found to be noncytotoxic.[41]

**Figure 1.10**. Examples of natural products containing *N*-Me-Val-Pro linkage.

## 1.3 Components of depsilairdin

### 1.3.1 Lairdinol A

#### 1.3.1.1 Isolation and characterization of lairdinol A

Lairdinol A was isolated in 2005 by Pedras and co-workers from the fungal (*L. maculans/P. lingam*) isolates Mayfair 2 and Laird 2.[19]

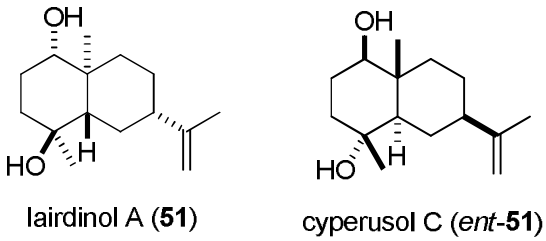



**Figure 1.11**. Structures of lairdinol A and its enantiomer, cyperusol C.

The enantiomer of lairdinol A, known as cyperusol C (*ent*-**51**), was isolated from two natural sources: the Egyptian herbal medicinal plant *Cyperus longus*[42] and *Erigeron annus*.[43] The absolute configuration of *ent*-**51** was assigned by Yoshikawa using the Mosher's ester method.

The structure of lairdinol A (**51**) was elucidated by using spectroscopic techniques.[19] Compound **51** indicated the presence of three distinct methyl singlets, an olefinic methylene and three methine protons which were determined by using $^{1}H$, $^{13}C$ NMR and HSQC. The spin systems were determined with the help of COSY and further correlations were deduced by using HMBC. Coupling constants and NOE helped in assigning out the relative configuration in lairdinol A (Figure 1.12). The proton at C-1 appeared at 3.11 ppm as a double of doublets ($J$ = 4, 11 Hz) suggesting a transdiaxial

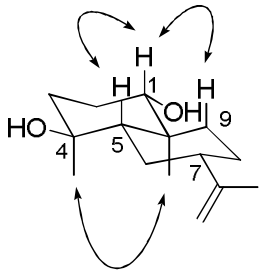



**Figure 1.12**. NOE correlations in lairdinol A (**51**).

relationship with one of the C-2 protons. Irradiation of HC-1 showed NOE with HC-5 & 9 and vice versa and the methyl singlets (at C-4 and C-10) showed NOE with each other confirming their relative syn orientation. The spectral data of cyperusol C (*ent*-**51**) as reported by Yoshikawa was taken in $CDCl_3$ while that of lairdinol A (**51**) was published in $C_6D_6$. The optical rotation, $^{1}H$ NMR and $^{13}C$ NMR of both natural products[19, 42] are given below for an immediate comparison (Table 1.2). Confirmation of the structures of

both **51** and *ent*-**51** by synthesis is one of the objectives of my current research en route to the total synthesis of depsilairdin.[†]

**Table 1.2.** Spectral data of lairdinol A (**51**) and cyperusol C (*ent*-**51**).

| **Lairdinol A ($C_6D_6$)** $[\alpha]_D$ = +18 (*c* 0.4, $CH_2Cl_2$)[a] | | **Cyperusol C ($CDCl_3$)** $[\alpha]_D$ = -42.3 (*c* 1.10, MeOH)[b] $[\alpha]_D$ = -25 (*c* 0.13, $CHCl_3$)[c] | |
|---|---|---|---|
| **$^1$H NMR** | **$^{13}$C NMR** | **$^1$H NMR** | **$^{13}$C NMR** |
| 4.96 (2H, d, *J* = 15 Hz, $H_2C$=C) | 150.6 (s, C=$CH_2$) | 4.72 (2H, m, $H_2C$=C) | 150.3 (s, C=$CH_2$) |
| 3.11 (1H, dd, *J* = 4, 11 Hz) | 108.8 (t, $CH_2$=C) | 3.32 (1H, dd, *J* = 4.4, 11.2 Hz, HC-4) | 108.3 (t, $CH_2$=C) |
| 2.03 (1H, m, HC-8) | 79.5 (d, C-4) | 1.94 (1H, m, HC-7) | 79.3 (d, C-4) |
| 1.95 (1H, m, HC-7) | 71.1 (s, C-1) | 1.90 (1H, ddd, *J* = 3.5, 3.5, 13.5, HC-5) | 71.6 (s, C-1) |
| 1.85 (1H, ddd, *J* = 3, 3, 13 Hz, HC-5) | 53.3 (d, C-8a) | 1.84 (1H, m, HC-8) | 52.9 (d, C-8a) |
| 1.82 (3H, s, $H_3CC$=C) | 46.4 (d, C-7) | 1.79 (1H, ddd, *J* = 3.0, 3.5, 12.0 Hz, HC-2) | 45.7 (d, C-7) |
| 1.67 (1H, m, HC-2) | 41.5 (t, C-2) | 1.75 (3H, s, $H_3CC$=C) | 40.8 (d, C-2) |
| 1.65 (1H, m, HC-6) | 41.0 (t, C-5) | 1.72 (1H, m, HC-3) | 40.5 (t, C-5) |
| 1.50 (1H, m, HC-3) | 39.3 (s, C-4a) | 1.62 (1H, m, HC-3) | 38.9 (s, C-4a) |
| 1.47 (1H, m, HC-6) | 29.2 (t, C-3) | 1.61 (1H, m, HC-6) | 28.5 (t, C-3) |
| 1.44 (1H, m, HC-3) | 27.0 (t, C-6) | 1.52 (1H, ddd, *J* = 3.5, 12.0, 13.5 Hz, HC-2) | 26.4 (t, C-6) |
| 1.38 (1H, m, HC-2) | 26.3 (t, C-8) | 1.38 (1H, dddd, *J* = 3.5, | 25.7 (t, C-8) |

[†] The spectral data of synthetic lairdinol A and natural products **51** and *ent*-**51** in different deuterated solvents will be discussed in more details on page 95.

| | | | |
|---|---|---|---|
| | | 13.0, 13.5, 17.0 Hz, HC-6) | |
| 1.30 (1H, ddd, *J* = 12, 12, 12 Hz, HC-8) | 22.9 (q, $CH_3C$-1) | 1.28 (1H, m, HC-8a) | 22.7 (q, $CH_3C$-1) |
| 1.15 (1H, dd, *J* = 2, 12 Hz, HC-8a) | 21.2 (q, $CH_3C$=C) | 1.26 (1H, m, HC-6) | 21.0 (q, CH3C=C) |
| 1.05 (1H, ddd, *J* = 3, 13, 13 Hz, HC-5) | 13.3 (q, $CH_3C$-4a) | 1.13 (1H, ddd, *J* = 4.0, 13.0, 13.5 Hz, HC-5) | 13.0 (q,$CH_3C$-4a) |
| 1.02 (3H, s, $H_3CC$-1) | | 1.11 (3H, s, $H_3CC$-1) | |
| 0.88 (3H, s, $H_3CC$-4a) | | 0.89 (3H, s, $H_3CC$-4a) | |

[a] Ref. 19, [b] Ref. 42, [c] Ref. 43

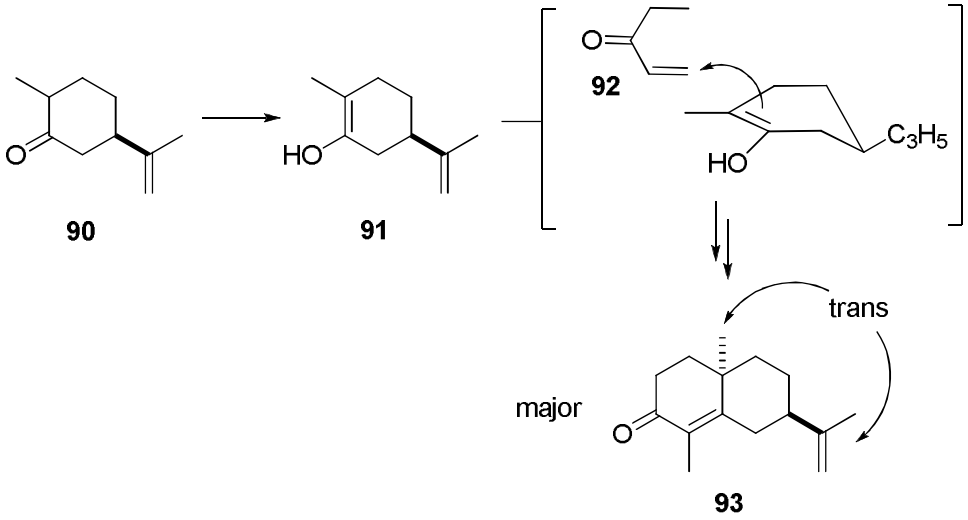
Lairdinol A has the same absolute configuration as the sesquiterpene fragment present in depsilairdin.[25] Interestingly, both natural products were isolated from the same fungal cultures in similar amounts and additionally, the fungus also produced metabolite selin-11-ene-4α-ol (**50**) which is structurally related to lairdinol A (Figure 1.3). Phytotoxicity studies revealed that **51** affected *B. juncea* causing leaf lesions while *B. napus* was unaffected at the same concentration.[19]

Lairdinol A (**51**) belongs to the eudesmane family of sesquiterpenes. This class of natural products has attracted considerable attention from synthetic chemists because of the challenge to construct the trans decalin ring junction. Some literature approaches to build such decalin systems are discussed below.

### 1.3.1.2 General synthetic approaches towards sesquiterpenes

Several strategies have been reported to synthesize eudesmane type sesquiterpenes. A common way to build the decalin systems involves Robinson annulation with dihydrocarvone (**90**) as starting material (Scheme 1.2).

**Scheme 1.2**. Synthesis of decalin blocks using Robinson annulation.

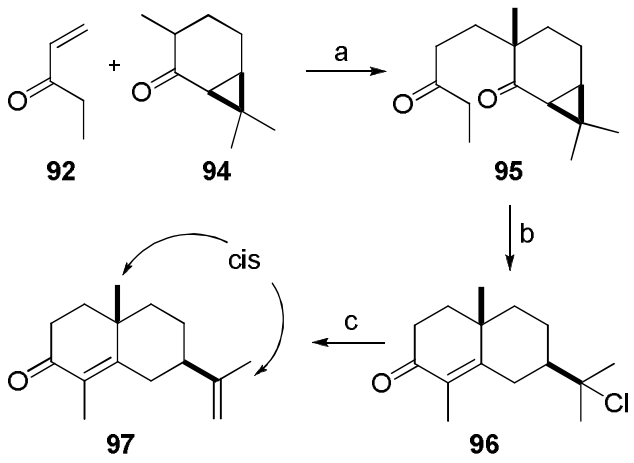



Compound **90** undergoes Robinson annulation with 1-pentene-3-one to give **93** as the major product, via an axial attack on the enolate double bond, producing a trans relationship between the angular methyl group and the isopropenyl group.[44] Although, many eudesmanes possess this relative configuration, this Robinson annulation approach is not appropriate for the synthesis of lairdinol A decalin system which has the angular methyl and the isopropenyl groups with a cis relative configuration.

There are several approaches documented in the literature to access the eudesmane skeleton with a cis relationship between the angular methyl and isopropyl groups. Caine *et al.* reported a Robinson annulation of (-)-2-carone (**94**), which is readily

available from (+)-dihydrocarvone, as a potential strategy to construct such carbocycles (Scheme 1.3).[45]

**Scheme 1.3**. Caine's approach.



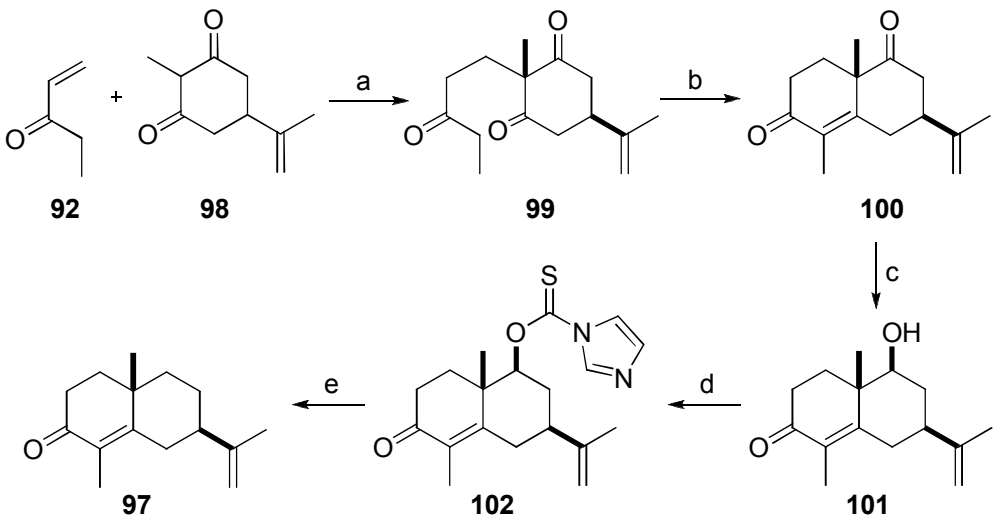

**Reagents and Conditions:** (a) KOH, EtOH, ether (72%); (b) EtOH, HCl (78%); (c) NaOAc, AcOH (82%).

Michael addition of the enolate of **94** with ethyl vinyl ketone (EVK, **92**) proceeded smoothly from the face opposite to the cyclopropane to give **95** as the sole isomer. When **95** was treated with ethanolic HCl, the cyclopropane ring opened and was trapped by a chloride ion to form the more stable 3$^{o}$ halide followed by intramolecular aldol condensation to afford **96**. Finally, dehydrohalogenation of **96** gave the desired (+)-α-cyperone **97**.[45]

Agami's approach commenced with the Michael reaction of oxycarvone **98** and EVK (**92**) to get adduct **99** followed by an organocatalyzed ring closure to **100**.[46] They carried out the intramolecular aldol reaction of **99** using (*S*)-phenylalanine to afford enantioenriched keto-enone **100**.[†] Finally, **100** was reduced and deoxygenated using the Barton-McCombie protocol to furnish (+)-α-cyperone **97** in good yield (Scheme 1.4).

[†] ee of **100** was 90-95% determined by $^{1}$H NMR using Eu(hfc)$_3$.

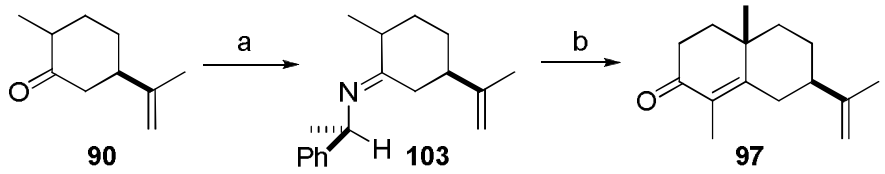
**Scheme 1.4**. Agami's approach.




**Reagents and Conditions:** (a) $H_2O$, MeOH, 50 $^oC$ (48% of **100**); (b) (*S*)-phenylalanine, 1N $HClO_4$, $CH_3CN$ (90%, ee = 90-95%); (c) $NaBH_4$, EtOH (91%); (d) 1,1'-thiocarbonyldiimidazole, $CH_2Cl_2$, reflux (86%); (e) $Bu_3SnH$, AIBN, toluene, reflux (82%).

de Groot *et al.* synthesized (+)-α-cyperone (**97**) from (+)-dihydrocarvone (**90**) via its imine derivative with (*R*)-phenylethylamine. It was noted that the imine **103** reacted with ethyl vinyl ketone from an axial orientation imposed by the chiral auxilliary present on the imine (Scheme 1.5). Compound **90** was converted to (+)-α-cyperone (**97**) in 47% overall yield without any intermediate purification. [47]

**Scheme 1.5**. de Groot's approach.



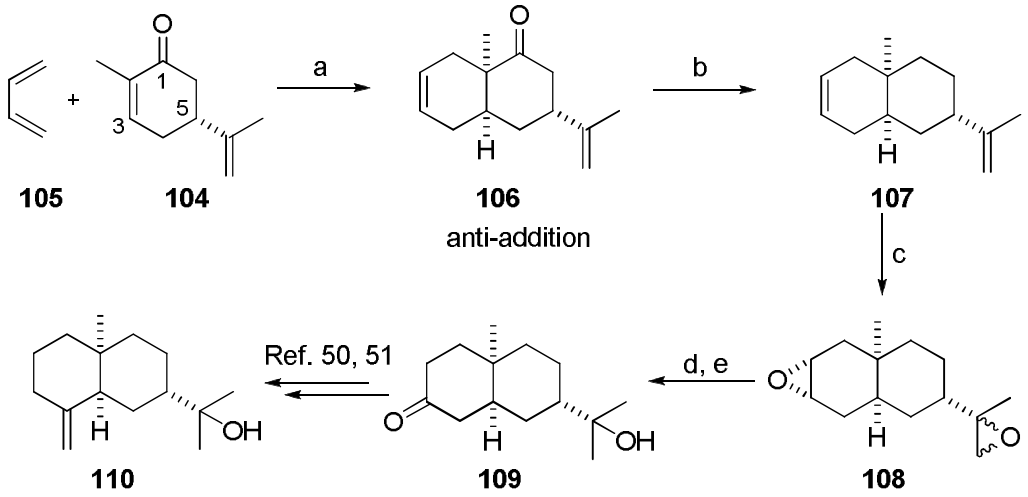

**Reagents and Conditions:** (a) (*R*)-phenylethylamine, toluene, reflux; (b) (I) EVK, THF, 40 $^oC$; (II) aq. AcOH; (III) NaOMe, MeOH (47%).

### 1.3.1.3 Diels-Alder approaches towards decalin systems

Harayama *et al.* were the first to report a Lewis acid catalysed Diels-Alder (DA) reaction of *R*-(-)-carvone (**104**) as a dienophile (Scheme 1.6).[48, 49] The DA reaction of carvone with 1,3-butadiene (**105**) in the presence of $AlCl_3$ gave DA adduct **106** in modest yield. The addition of the diene took place anti to the substituent at the C-5 position in carvone, installing the angular methyl group and the isopropenyl group cis to each other. The cycloadduct **106** was subsequently was utilized to synthesize (-)-*β*-eudesmol from **109**.

The cis-decalin **106** was deoxygenated and epoxidized to the bis-epoxide **108** in 25% yield over two steps. Reductive openings of the mixture of epoxides were achieved with $LiAlH_4$ followed by oxidation of the secondary alcohol to give keto-alcohol **109**. The enantiomer of **109** was previously transformed into (+)-*β*-eudesmol,[50, 51] hence Harayama reported his synthesis of **110** as a formal approach.

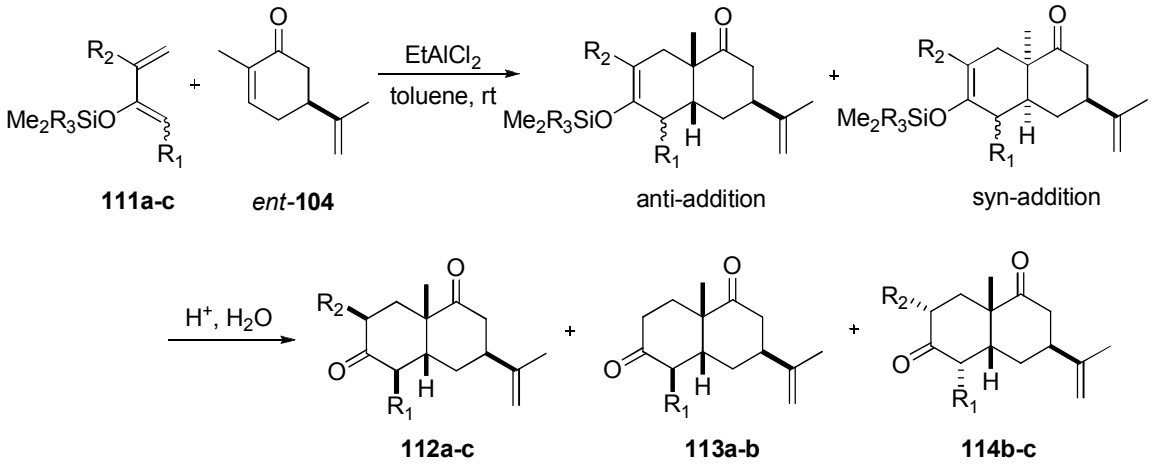
**Scheme 1.6**. Synthesis of (-)-*β*-eudesmol.




**Reagents and Conditions:** (a) $AlCl_3$, benzene (40%); (b) *p*-$TsNHNH_2$, $NaBH_4$; (c) *m*-CPBA (25% over two steps); (d) $LiAlH_4$; (e) Jones' oxidation (65% two steps).

Although the DA reaction between carvone and 1,3-butadiene occurred smoothly, the corresponding adduct is not ideally functionalized. The use of a more functionalized diene e.g. Danishefsky's diene[52] (trans-1-methoxy-3-trimethylsiloxy-1,3-butadiene), unfortunately, gave desilylated products with poor selectivities and yields.[53] de Groot has reported the DA reactions of (*S*)-(+)-carvone (*ent*-**104**) with functionalized dienes such as 2-trimethylsilyloxy-1,3-butadiene (**111a**), 3-trimethylsilyloxy-1,3-pentadiene (**111b**) and 2-*tert*-butyldimethylsilyloxy-3-methyl-1,3-butadiene (**111c**) that are stable to the reaction conditions (Scheme 1.7).[54] $EtAlCl_2$ was found to be the most effective catalyst for the DA reaction. When dienes **111a-c** were reacted with (*S*)-(+)-carvone (*ent*-**104**) in the presence of 0.5 equiv. of $EtAlCl_2$, the adducts resulting from anti addition were predominant (Table 1.3)

**Scheme 1.7**. Diels-Alder approach towards sesquiterpenes.




a. $R_1 = R_2 = H$, $R_3 = Me$; b. $R_1 = Me$, $R_2 = H$, $R_3 = Me$; c. $R_1 = H$, $R_2 = Me$, $R_3 = t$-Bu

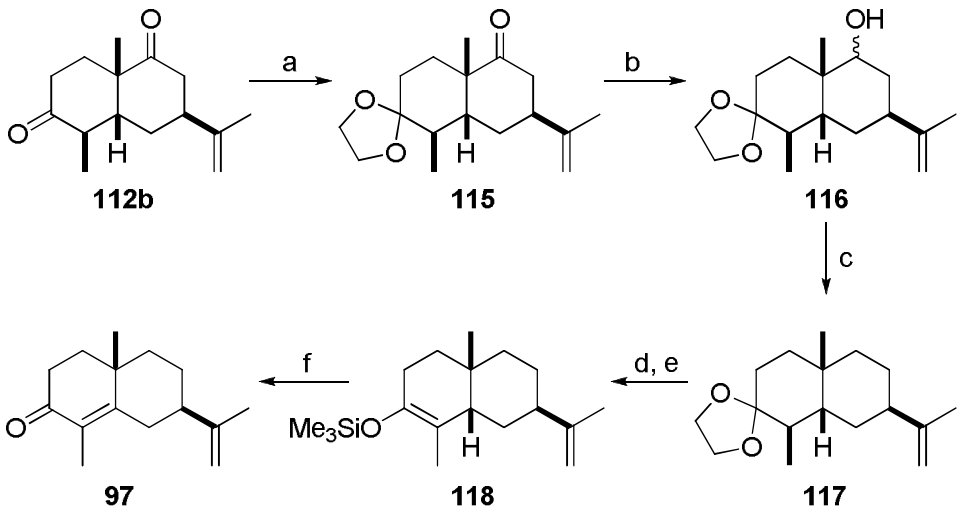
**Table 1.3**. Product distribution of DA adducts from the reaction of *ent*-**104** and **111a-c**.

| Diene | Products | Ratio | % Anti-addition | Product yield[a] |
|---|---|---|---|---|
| **111a** | **112a, 113a** | 19:1 | 95 | 73 |
| **111b** | **112b, 113b, 114b** | Variable[b] | 91 | 77 |
| **111c** | **112c, 114c** | 10:11 | 100 | 74 |

[a]Isolated yield after desilylation.
[b]Epimerization of **114b** to **112b** took place upon hydrolysis.

Epimerization studies on substrates **112b** and **114b** showed that **114b** was completely converted to **112b** using sodium methoxide. Under optimized conditions, compound **112b** was obtained in 69% yield after epimerization and was transformed into (+)-α-cyperone (Scheme 1.8).[54] The more easily accessible carbonyl group in **112b** was

**Scheme 1.8**. Synthesis of (+)-α-cyperone.



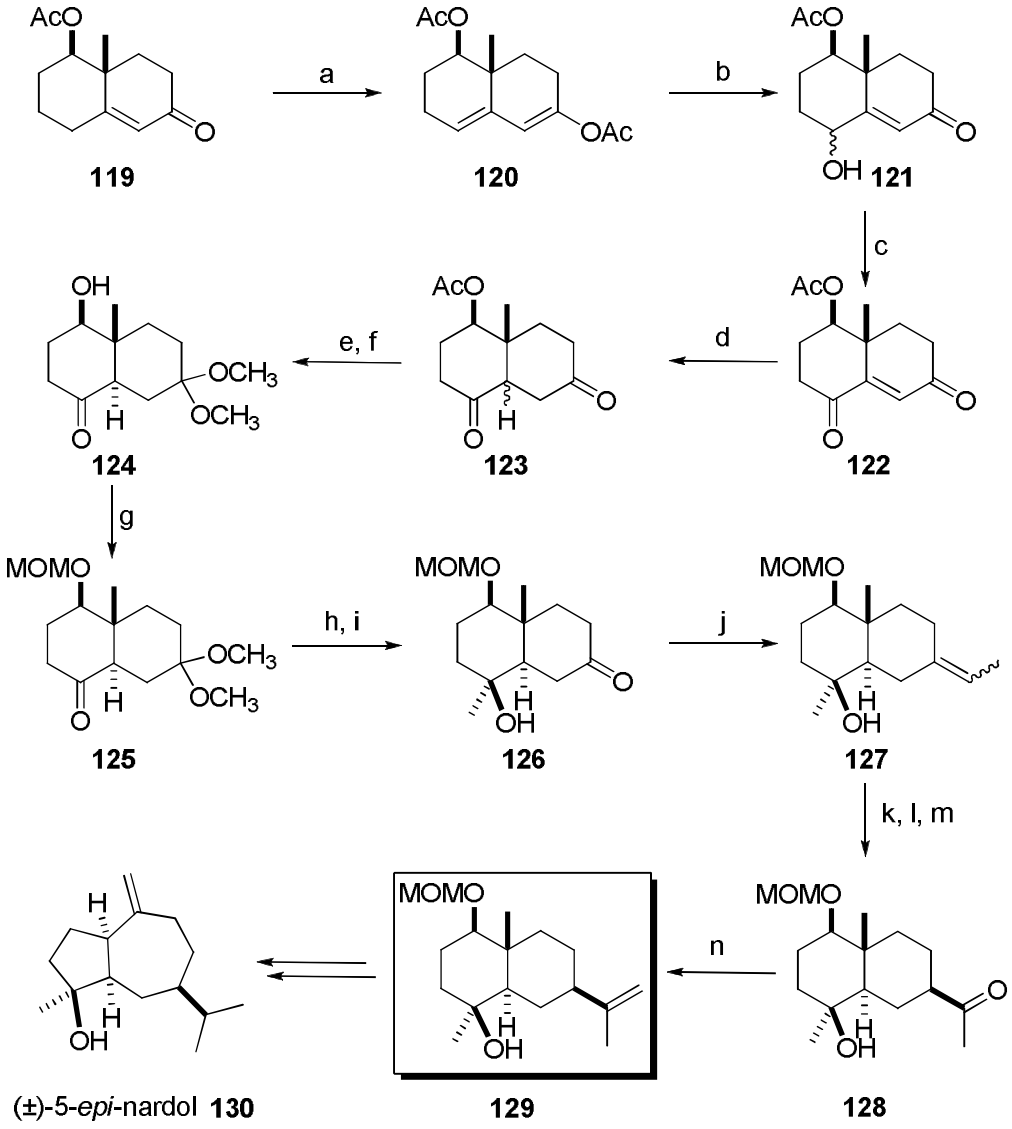

**Reagents and Conditions:** (a) MED, PTSA, glycol (97%); (b) $LiAlH_4$, ether (96%); (c) (I) NaH, $CS_2$, MeI, THF, reflux; (II) $Bu_3SnH$, AIBN, Toluene, reflux (86%); (d) $H^+$, $H_2O$, acetone; (e) TMSCl, $Et_3N$, DMF (90% two steps); (f) DDQ, benzene (87%).

selectively protected as an acetal followed by $LiAlH_4$ reduction to give epimeric alcohols **116** that coalesce to **117** in good yield using the Barton McCombie deoxygenation protocol. Finally, a sequence of acetal deprotection, silyl enol ether formation and DDQ treatment afforded (+)-α-cyperone (**97**).[54]

### 1.3.1.4 de Groot's synthesis of a diastereomer of lairdinol A

A key intermediate in the synthesis of (±)-5-*epi*-nardol (**130**) is the racemic **129**, a protected diastereomer of lairdinol A (**51**) (Scheme 1.9).[55, 56] The synthesis began from easily accessible enone **119** (prepared from Wieland-Miescher ketone) that was converted to dienol-acetate **120**. An important feature in **129** (and **51**) is the trans fused ring junction and this issue was carefully addressed at an early stage in de Groot's synthesis. Oxidation of **120** at the C-8 position using *m*-CPBA furnished **121** as a mixture of diastereomeric alcohols in 76% combined yield. At this stage, stereoselective reduction of the enone in **121** was planned in order to set the trans ring junction. Unfortunately, attempts to reduce the alkene via catalytic hydrogenation led to the formation of complex unidentified reaction mixtures while lithium ammonia reduction led to the elimination of the hydroxyl group. To avoid elimination, **121** was oxidized to the corresponding diketone **122** followed by reduction using $TiCl_3$ to successfully afford a 2:1 mixture of cis and trans isomers of **123** in 95% yield. Regioselective protection of the less hindered ketone in **123** as its acetal and subsequent isomerization with sodium methoxide furnished deacetylated trans decalin **124** as a single diastereomer. MOM protection and addition of a methyl nucleophile to **125** delivered **126** after removal of the acetal group.

**Scheme 1.9**. de Groot's synthesis of a diastereomer of lairdinol A.




**Reagents and Conditions:** (a) $Ac_2O$, cat. $H_2SO_4$ (80%); (b) *m*-CPBA, dioxane (68%); (c) PCC/alumina, benzene (54%); (d) $TiCl_3$ (95%); (e) $(CH_3O)_3CH$, PTSA (72%); (f) NaOMe, MeOH (95%); (g) MOMCl, DIEA, $CH_2Cl_2$ (96%); (h) $CH_3MgI$, ether; (i) PPTS, acetone, $H_2O$ (92% two steps); (j) $Ph_3P{=}CHCH_3$, DMSO (88%); (k) $B_2H_6$, $H_2O_2$/NaOH; (l) NDC, py, benzene; (m) $NaOCH_3$. $CH_3OH$ (58% three steps); (n) $Ph_3P{=}CH_2$, DMSO (78%).

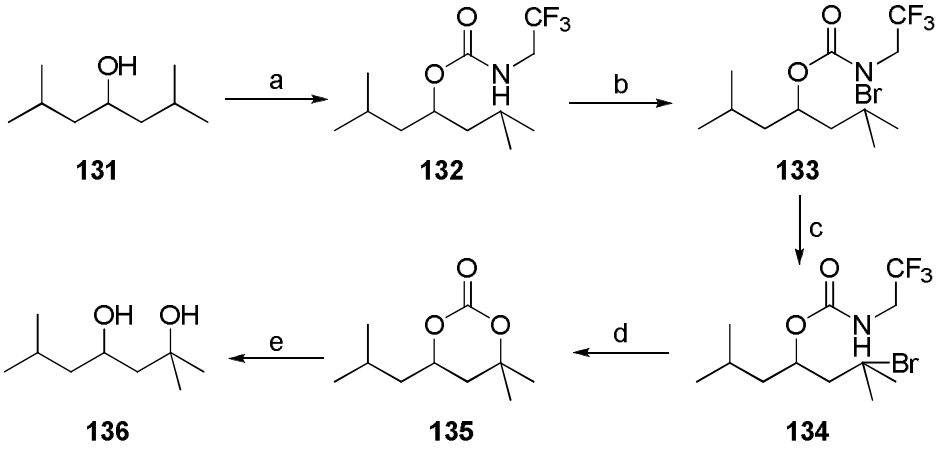
Introduction of the isopropenyl group in **126** was achieved by a sequence of Wittig olefination followed by hydroboration and oxidation to give a mixture of diasteromeric ketones that were subsequently isomerized using NaOMe to give a single

diastereomer of **128**. Finally, Wittig reaction using $CH_2$=$PPh_3$ gave the protected racemic **129** (a MOM derivative of the C-4 epimer of lairdinol A) which was then transformed into (±)-5-*epi*-nardol (**130**).[55]

### 1.3.1.5 Baran's synthesis of hydroxylated eudesmanes

Recently, Baran and co-workers have reported the synthesis of 1,3-diols via site selective C-H oxidations (Scheme 1.10).[57] Baran's work was inspired by the Hofmann-Loffler-Freytag (HLF) reaction, known to intramolecularly halogenate C-H bonds.[58] Formation of the 1,3-diol was challenged by two facts; (a) selective formation of the alkyl bromide from the corresponding *N*-bromocarbamate and, (b) cyclization of the carbamate at the oxygen centre rather than the nitrogen centre.

**Scheme 1.10**. Baran's synthesis of 1,3-diols.



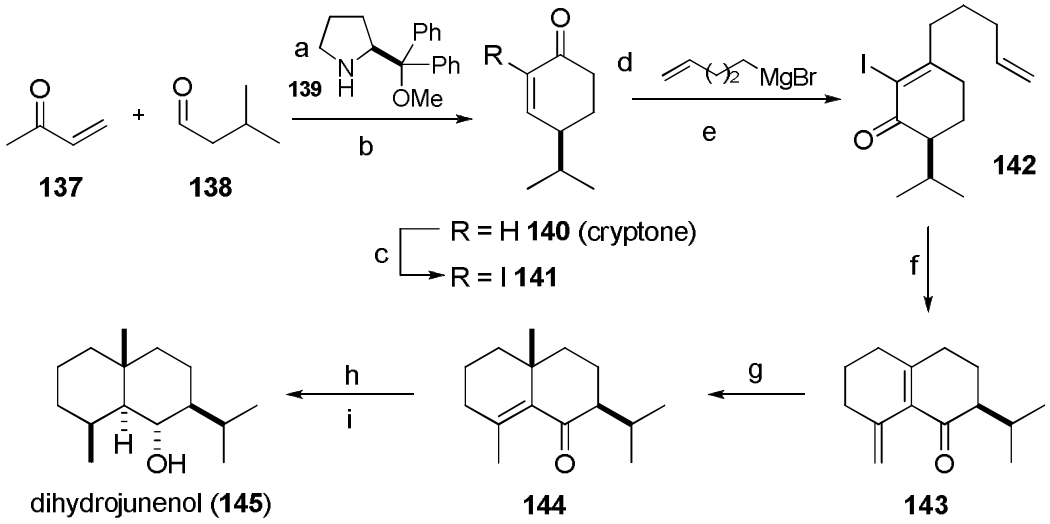

**Reagents and Conditions:** (a) $CF_3CH_2NCO$, $CH_2Cl_2$, Py (97%); (b) $CH_3CO_2Br$, $CH_2Cl_2$; (c) $PhCF_3$, $CBr_4$, hv; (d) $Ag_2CO_3$, $CH_2Cl_2$, then AcOH; (e) $K_2CO_3$, MeOH (69% over 4 steps).

The first obstacle was tackled by studying different carbamates and it was found that the use of trifluoroethyl carbamate was essential to get synthetically useful amounts

of the corresponding alkyl halide (**134**). The second challenge was defeated by the use of $Ag_2CO_3$ to give the desired cyclized product (**135**), which was subsequently hydrolyzed to furnish 1,3-diol (**136**) in good yield.[57]

With an efficient access to 1,3-diols delineated, Baran applied this protocol to the synthesis of hydroxylated eudesmanes.[59]

**Scheme 1.11**. Baran's synthesis of eudesmane (**145**).

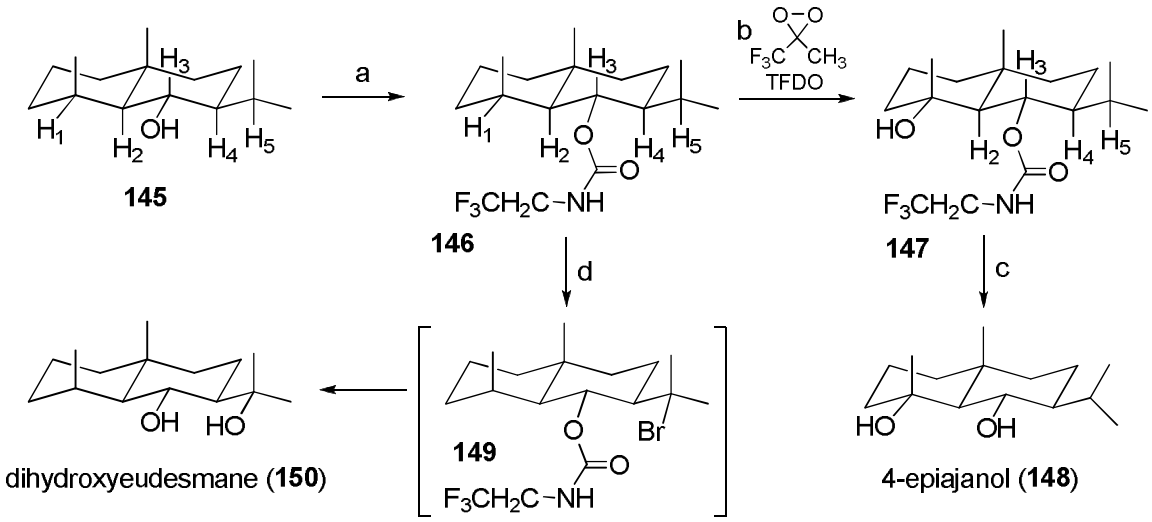



**Reagents and Conditions:** (a) MVK, 3-methylbutyraldehyde, proline (**139**) (0.05 equiv.), ethyl-3,4-dihydroxybenzoate, neat; (b) LiOH, $^{i}$PrOH, rt (63% over 2 steps, 89% ee); (c) $I_2$, Py/$CH_2Cl_2$ (99%); (d) $CH_2CHCH_2CH_2CH_2MgBr$, toluene; (e) PCC, 3 Å MS, $CH_2Cl_2$ (74% over 2 steps); (f) $Pd(OAc)_2$, $PPh_3$, $Et_3N$, $Ag_2CO_3$, $CH_3CN$, 70$^{o}$C (95%); (g) $LiMe_2Cu$, $CH_2Cl_2$, 0$^{o}$C (56%); (h) $H_2$, Pd/C, EtOAc; (i) Na, EtOH, rt (87% over 2 steps).

The synthesis commenced with commercially available MVK (**137**) and 3-methyl butyraldehyde (**138**). Intermolecular Michael reaction of **138** with **137** in the presence of proline **139** followed by base treatment led to the formation of cryptone (**140**) in 63% yield (89% ee). Enone **140** was subsequently iodinated to iodoenone **141**. Addition of homoallylic Grignard reagent to **141** followed by 1,3-carbonyl transposition provided **142**. Next, intramolecular Heck reaction proceeded smoothly to furnish the decalin **143**

in good yield. Introduction of the angular methyl group was achieved by treating **143** with $Me_2CuLi$. Finally, a sequence of hydrogenation and reduction furnished the natural product, dihydrojunenol (**145**), having a trans ring junction (similar to that in lairdinol A). Compound **145** sets the stage for hydroxylation steps.

**Scheme 1.12**. Synthesis of dihydroxylated eudesmanes.



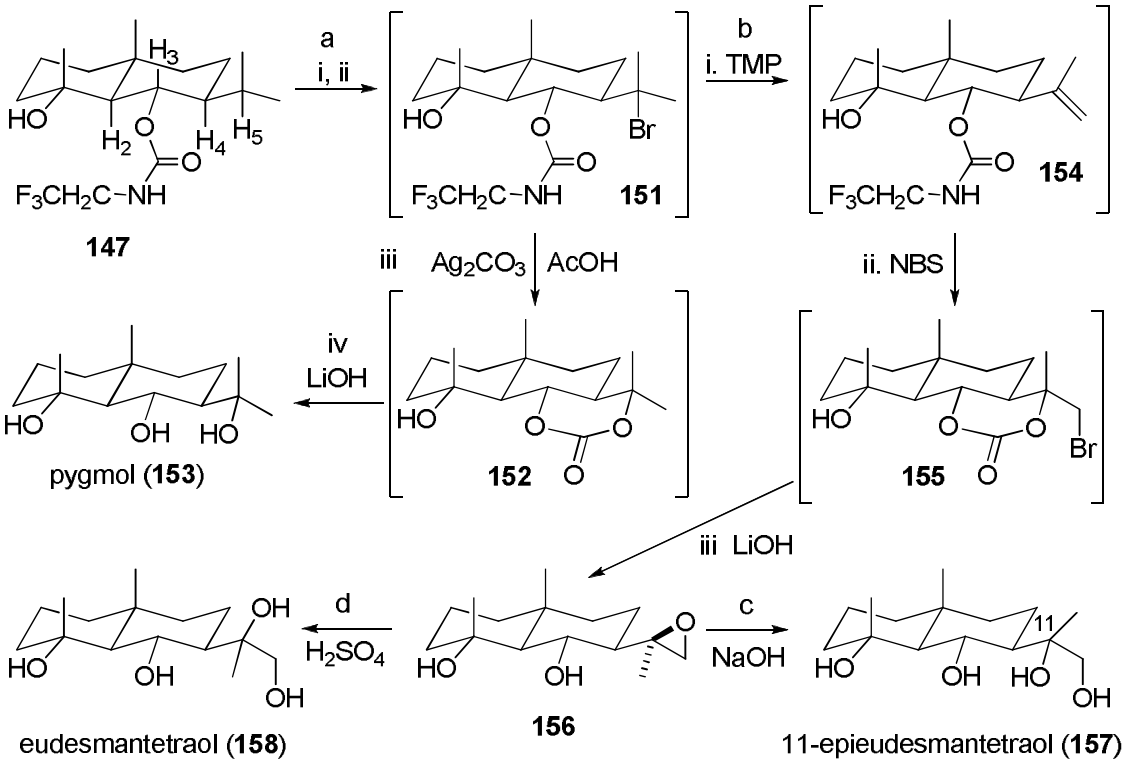

**Reagents and Conditions:** (a) $CF_3CH_2NCO$, Py, DMAP, $CH_2Cl_2$ (99%); (b) TFDO, $CH_2Cl_2$ (82%); (c) NaOMe, MeOH (95%); (d) $CH_3CO_2Br$, $CH_2Cl_2$; $PhCF_3$, 100W sunlamp; $Ag_2CO_3$, $CH_2Cl_2$; LiOH, $THF/H_2O$ (43%, 39% recovered **145**).

Alcohol **145** was converted to its trifluoroethyl carbamate **146** which in turn was subjected to oxidation to give **147** with the desired oxidation at the $H_1$ position; subsequent hydrolysis gave 4-epiajanol (**148**). However, to functionalize the $H_5$ position, carbamate **146** was subjected for halogenation leading to alkyl bromide **149**.[59] Finally, silver carbonate mediated cyclization followed by hydrolysis furnished dihydroxyeudesmane (**150**) (Scheme 1.12).

Synthesis of eudesmanes with higher oxidation states containing three or four hydroxyl groups was envisaged starting with **147**. Carbamate **147** was converted to its

alkyl bromide **151** followed by cyclization using $Ag_2CO_3$. Finally, hydrolysis using lithium hydroxide gave pygmol (**153**).[59]

**Scheme 1.13**. Synthesis of tri and tetrahydroxyeudesmanes.




**Reagents and Conditions:** (a) i. $CH_3CO_2Br$, $CH_2Cl_2$; $PhCF_3$, ii. 100W sunlamp; iii. $Ag_2CO_3$, $CH_2Cl_2$, then aq. AcOH, iv. LiOH, THF/$H_2O$, rt (52%, 30% recovered **147**); (b) i. TMP, toluene; ii. NBS, $CH_2Cl_2$ then aq. AcOH; iii LiOH, THF/$H_2O$ (27%, 37% recovered **147**); (c) 3M NaOH, DMSO (90%); (d) 0.1M $H_2SO_4$, DME/$H_2O$ rt (87%).

To obtain a eudesmane unit with four alcohol groups, bromide **151** was converted to alkene **154**. Dihydroxylation of **154** using Sharpless AD-mixes or $OsO_4$ were ineffective. In an attempted reaction, alkene **154** was reacted with NBS followed by aqueous acetic acid treatment to afford bromocarbonate **155**. Hydrolysis of **155** gave epoxide **156** which was converted to either eudesmantetraol (**158**) using 0.1 M $H_2SO_4$ or to 11-epieudesmantetraol (**157**) using 3M NaOH (Scheme 1.13).[59]

### 1.3.2 (2*S*,3*S*,4*R*)-3,4-Dihydroxy-3-methylproline

The novel (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline (**58**) is an important constituent of depsilairdin (**55**). Various hydroxylated prolines are constituents of natural products [e.g. (2*S*,3*R*)-3-hydroxy-3-methylproline (**163**) is present in polyoxypeptins A and B (*vide infra*)] and have been synthesized to determine their biological profiles (Figure 1.13).

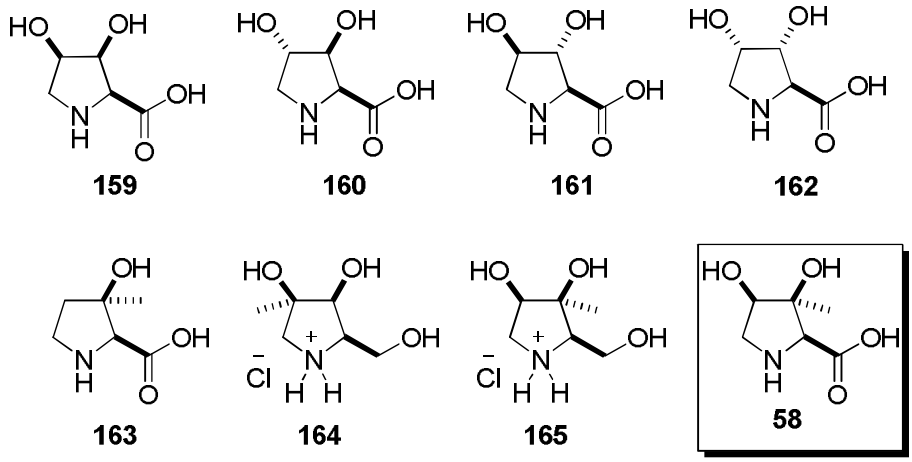



**Figure 1.13**. Hydroxylated prolines structurally related to **58**.

(2*S*,3*S*,4*R*)-3,4-Dihydroxy-L-proline **(159)** and (2*S*,3*S*,4*S*)-3,4-dihydroxy-L-proline **(160)** were found to have glycosidase inhibitor activities whereas (2*S*,3*S*,4*R*) diastereomer **161** is present in an animal adhesive protein.[60] In search for potential glycosidase inhibitors having potential anticancer and antiviral profiles, Sardina has reported the syntheses of **164** and **165** from *trans*-4-hydroxy-L-proline; notably, triol **165** is closely related in structure to **58**.[61, 62] The potential glycosidase inhibitor activities of hydroxyprolines has attracted considerable synthetic interest from chemists who have

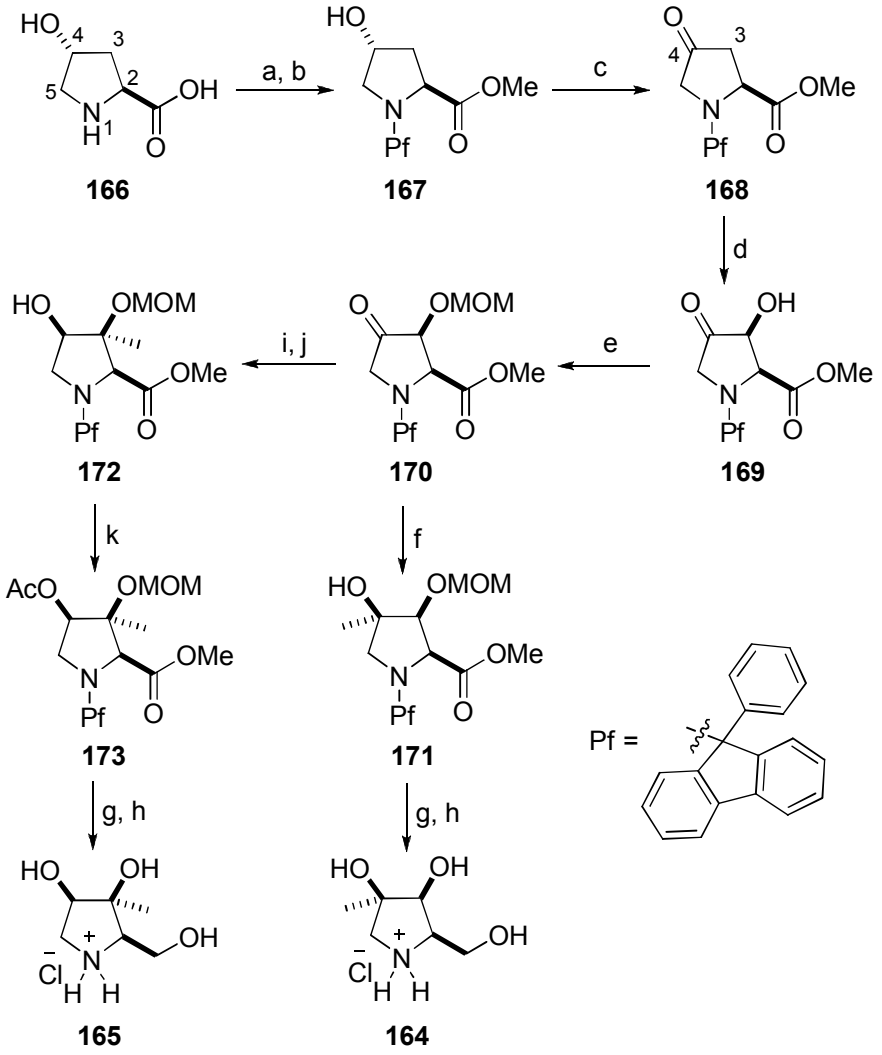
developed several elegant approaches towards their preparation; a few selected syntheses are discussed below.

### 1.3.2.1 Sardina's synthesis of triol 165

Sardina's synthesis commenced with commercially available *trans*-4-hydroxy-L-proline (**166**) (Scheme 1.14).[61, 62] Important features of this approach involved oxidation of the hydroxyl group at C-4 position to provide ketone **168** which was utilized to introduce the hydroxyl and methyl groups at C-3. Sardina and coworkers used the 9-phenylfluoren-9-yl (Pf) protecting group for the proline nitrogen. It is known that the steric bulk of the Pf group suppresses deprotonation at the C-2 and C-5 positions, thereby preserving the stereochemical integrity at C-2 and promoting a regioselective deprotonation at the C-3 position of **168**.[63] Moreover, molecular mechanics calculations on various *N*-Pf-$\Delta^{3,4}$-dehydroproline model systems suggested that the ester group at the C-2 position is locked in a pseudo axial position that blocks the top face of the enolate.[62]

The synthesis of the desired triols **164** and **165** began with esterification of **166**, followed by *N*-alkylation using PfBr and then Swern oxidation to furnish **168** in high yield. Regioselective enolization of **168** was best achieved with NaHMDS followed by oxidation using MoOPH to give alcohol **169**. The secondary alcohol in **169** was protected as its MOM ether in order to effect subsequent transformations. The resulting **170** nicely sets the stage for the incorporation of a methyl group either at C-3 position using enolization/methylation chemistry or at C-4 position by nucleophilic addition of a methyl group. To access **164**, when $CH_3Li$ was used as a source of a methyl group, **171** was obtained in modest yields along with starting ketone **170**. Quenching of the reaction

**Scheme 1.14**. Sardina's synthesis of triols **164** and **165**.




**Reagents and Conditions:** (a) $SOCl_2$, MeOH; (b) TMSCl, $Et_3N$, MeOH, PfBr, $Pb(NO_3)_2$, $CH_2Cl_2$ (82% two steps); (c) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$ (100%); (d) NaHMDS, MoOPH, THF (82%); (e) MOMCl, imidazole, DMF (96%); (f) MeMgBr, THF (94%); (g) $LiBH_4$, THF; (h) $H_2$, Pd/C, MeOH, HCl (90% two steps); (i) *n*-BuLi, HMPA, MeI, THF; (j) $NaBH_4$, MeOH. THF (62% two steps); (k) Py, $Ac_2O$ (91%).

mixture with $D_2O$ showed substantial deuterium incorporation at C-3 indicating that $CH_3Li$ was partly acting as a base. Interestingly, the C-3 diastereomer of **170** was not detected, suggesting that the putative enolate was reprotonated stereoselectively. Alternatively, compound **170** was treated with MeMgBr to access **171** that was subsequently reduced and hydrogenolyzed under acidic conditions to provide **164**.[62]

The triol **165,** which is analogous to the depsilairdin fragment (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline (**58**), was also synthesized from **170**. The regioselective methylation at C-3 of **170** was best achieved using *n*-BuLi/MeI,[†] that was followed by reduction to furnish **172** in 62% yield over two steps.[¶] A sequence of acetylation, $LiBH_4$ reduction and hydrogenation over Pd/C gave **165** in satisfactory yields.[62]

### 1.3.2.2 Summary of syntheses of (2*S*,3*R*)-3-hydroxy-3-methylproline

Polyoxypeptins A (**174**) and B (**175**) were isolated by Umezawa *et al.* in 1998 from Streptomyces cultures (Figure 1.14). Polyoxypeptin A is known to induce apoptosis in human pancreatic carcinoma AsPC-1 cells. Both polyoxypeptins contain six different amino acids of which (2*S*,3*R*)-3-hydroxy-3-methylproline (**163**) was observed for the first time in these natural products.[64, 65]

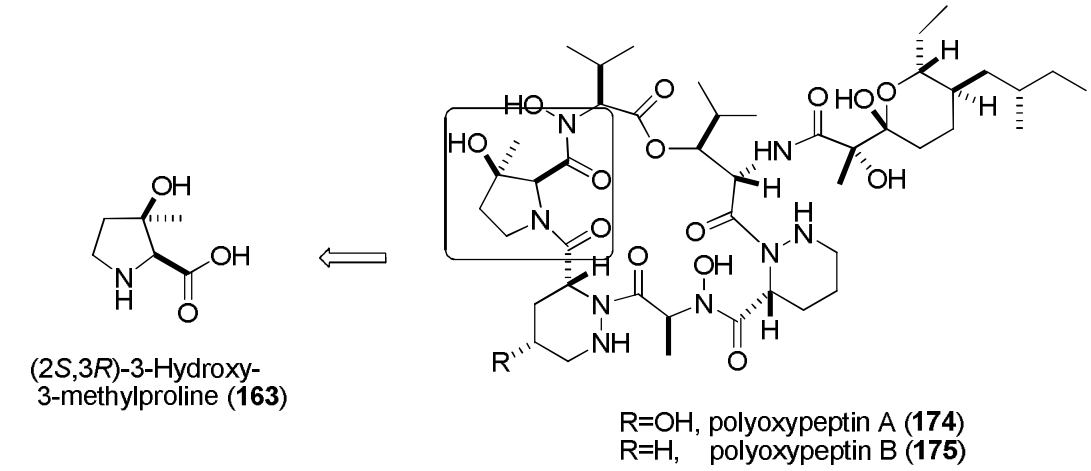



**Figure 1.14**. Structures of (2*S*,3*R*)-3-hydroxy-3-methylproline, polypeptins A and B.

[†] Other bases such as NaHMDS gave decomposition.

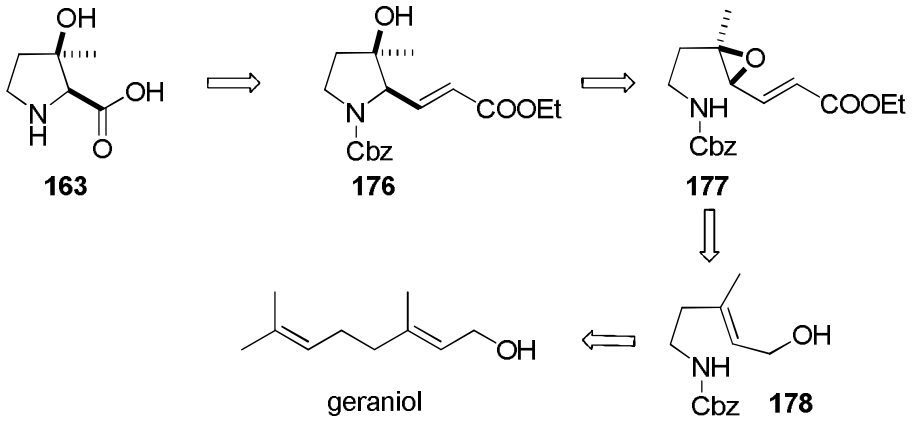
[¶] No side products were reported.

Since its discovery, several successful syntheses of (2*S*,3*R*)-3-hydroxy-3-methylproline have been reported. Kobayashi *et al.* were the first to synthesize the amino acid **163** starting from geraniol.[66] After this report, the groups of Hamada,[67-71] Yao,[72, 73] Merino,[74] Davis[75] and Ye[76] also successfully reported the preparation of (2*S*,3*R*)-3-hydroxy-3-methylproline and selected syntheses are described below.

**Kobayashi's Synthesis**

Kobayashi's strategy for the synthesis of **163** is illustrated in Scheme 1.15. The carboxylic acid group at C-2 position on the pyrrolidine ring was obtained from oxidative cleavage of the double bond in **176**. The success of this strategy mainly relied on the Pd-catalyzed cyclization of **177** which in turn was synthesized from geraniol via an enantioselective Sharpless epoxidation.[66]

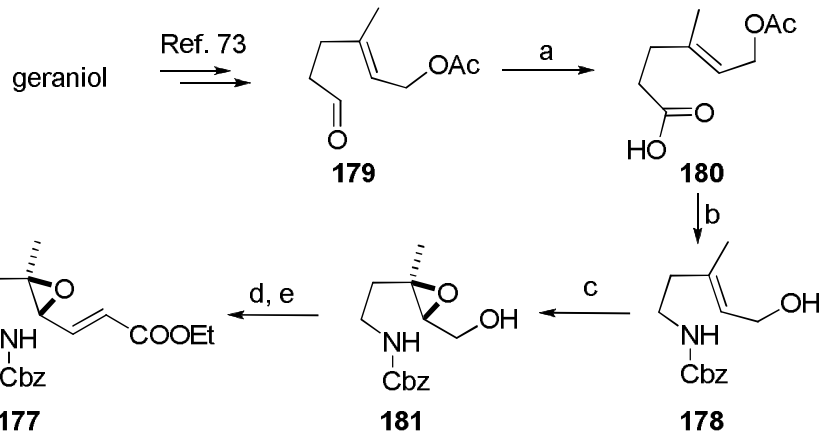
**Scheme 1.15**. Kobayashi's synthetic strategy.




Aldehyde **179**[77] was transformed into the carboxylic acid **180** using $NaClO_4$. Curtius rearrangement of **180** followed by treatment with BnOH under reflux conditions and hydrolysis afforded epoxide **181** in good yield after Sharpless epoxidation. Swern

oxidation of epoxy-alcohol **181** followed by Wittig reaction using a stabilized Wittig reagent [$(EtO)_2P(O)(CH_2COOEt)$] gave exclusively trans-alkene **177** which now set the

**Scheme 1.16**. Synthesis of **177**.




**Reagents and Conditions:** (a) $NaClO_4$, 2-methyl-2-butene, *t*-BuOH-$H_2O$, (96%); (b) (i) $(PhO)_2P(O)N_3$, $Et_3N$, benzene, then BnOH (ii) $K_2CO_3$, MeOH, (67%); (c) TBHP, $Ti(O^iPr)_4$, *D*-(-)-DET, 4Å MS, $CH_2Cl_2$ (55%, 97% ee); (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$; (e) $(EtO)_2P(O)(CH_2COOEt)$, NaH, THF (58% 2 steps).

stage for the Pd-catalyzed cyclization (Scheme 1.16). When **177** was subjected to $Pd(PPh_3)_4$/NaH no cyclization was observed at room temperature while a complex mixture was obtained under refluxing conditions. However, in the absence of base, desired product **176** along with its C-2 epimer in a 9:1 ratio were both obtained (see Figure 1.15 for a proposed mechanism).[66]

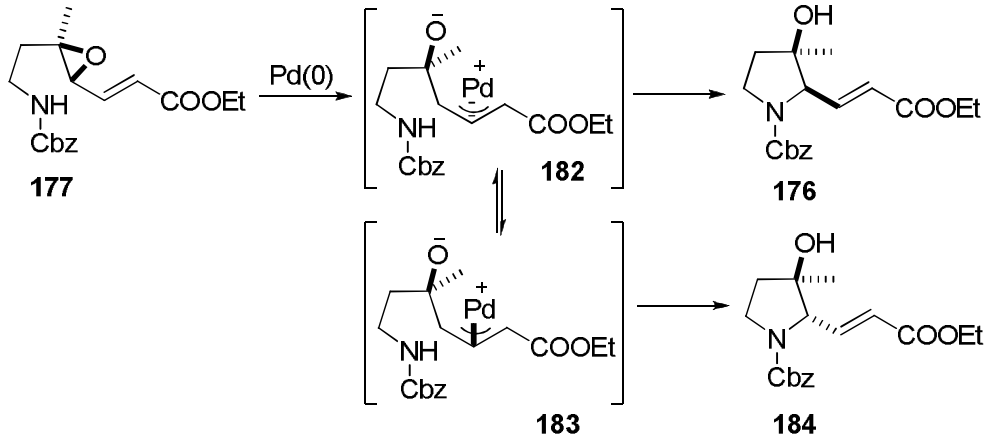
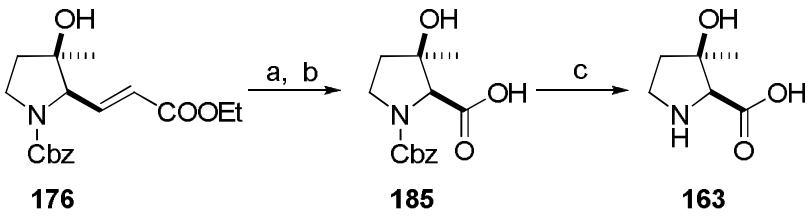



**Figure 1.15**. Proposed mechanism for Pd-catalyzed cyclization.

**Scheme 1.17**. Completion of the synthesis of **163**.



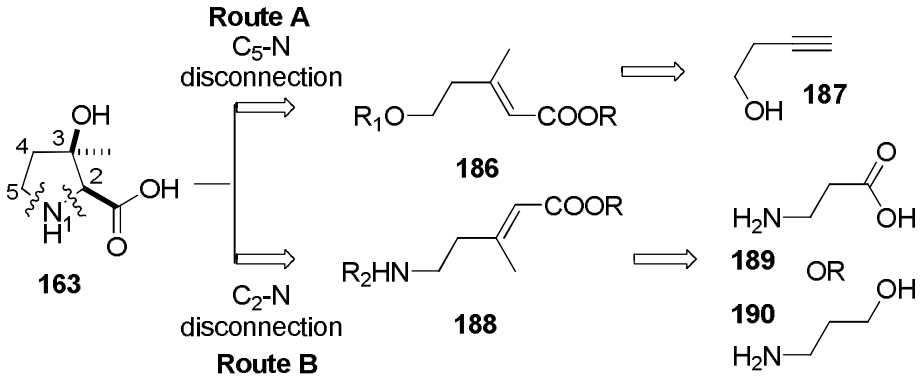

**Reagents and Conditions:** (a) $O_3$, MeOH, $Me_2S$ (82%); (b) $NaClO_4$, $NaH_2PO_4$, 2-methyl-2-butene, *t*-BuOH, $H_2O$ (88%); (c) $H_2$, Pd/C, MeOH (100%).

Compound **176** was then subjected to ozonolysis followed by oxidation to furnish acid **185** in 72% yield over two steps. Finally, Cbz deprotection provided the desired (2*S*,3*R*)-3-hydroxy-3-methylproline **163** (Scheme 1.17).

## Yao's Synthesis

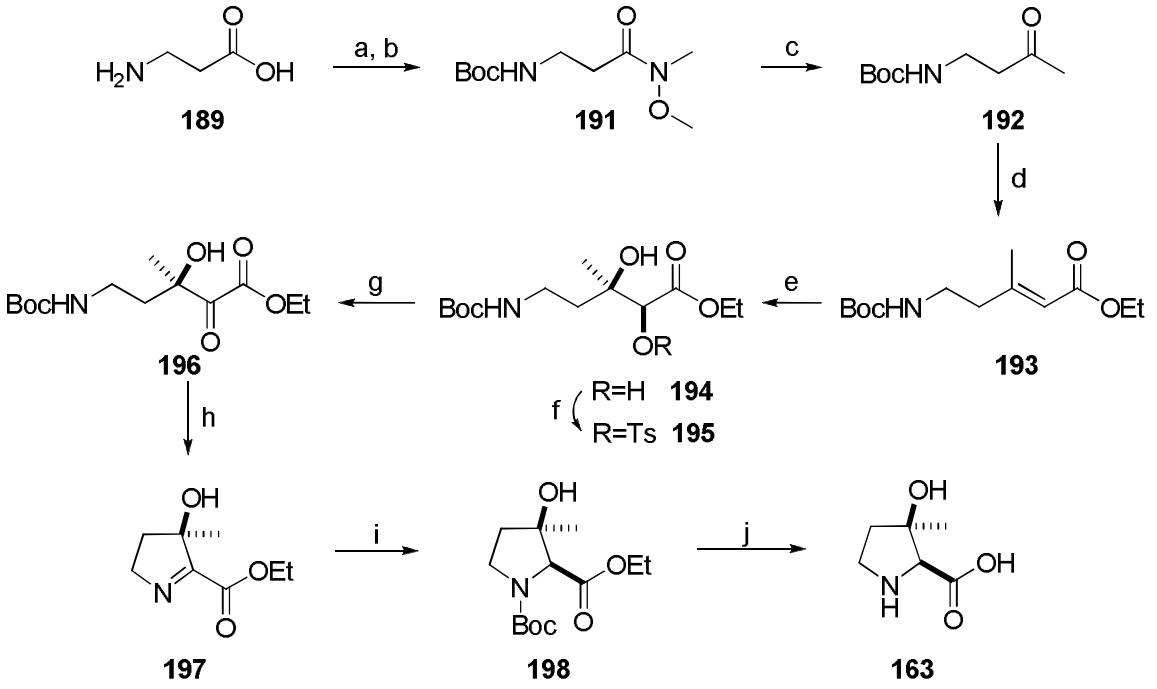
Yao's retrosynthetic analysis for the synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**163**) is shown in Scheme 1.18. Two possible pathways via $C_5$-N and $C_2$-N bond disconnections are described. In the synthesis via route A, the main reactions involved were Sharpless asymmetric dihydroxylation and regioselective opening of a cyclic sulfate by sodium azide.[72]

**Scheme 1.18**. Yao's synthetic strategy.



The synthesis via route B began with Boc protection of 3-aminopropanoic acid **189** followed by Weinreb amide formation to furnish **191** in good yield (Scheme 1.19). Addition of MeMgBr to **191** afforded ketone **192**, which was subsequently homologated to $\alpha,\beta$-unsaturated ester **193** via a Wittig protocol. Sharpless asymmetric dihydroxylation of **193** using AD-mix-$\beta$ furnished diol **194**.[†] Oxidation of **194** using PDC or Dess-Martin periodinane led to diol cleavage to give ketone **192** but when oxidation was carried out under Swern conditions, keto-ester **196** was obtained in good yield. Boc deprotection

**Scheme 1.19**. Yao's synthesis of **163**.




**Reagents and Conditions:** (a) $(Boc)_2O$, $K_2CO_3$, $H_2O$, Dioxane (98%); (b) (I) MeOH, $(MeO)_3CH$, $H_2SO_4$, reflux, 18 h; (II) Me(MeO)NH·HCl, $^{i}$PrMgCl, THF −15°C-rt, (80%); (c) MeMgI, THF (72%); (d) $(EtO)_2P(O)(CH_2COOEt)$, NaH, THF (66%); (e) AD-mix-$\beta$, $CH_3SO_2NH_2$, *t*-BuOH-$H_2O$ (89%); (f) TsCl, $Et_3N$, $CH_2Cl_2$ (82%, ee = 98%); (g) DMSO, $(COCl)_2$, $CH_2Cl_2$ (88%); (h) TFA, $CH_2Cl_2$, then $Et_3N$, $CH_2Cl_2$ (81%); (i) $(Boc)_2O$, EtOH, 10% Pd/C (78%); (j) LiOH·$H_2O$, then TFA, $CH_2Cl_2$ (81%).

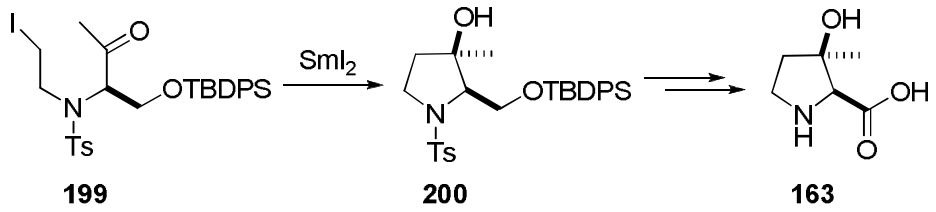
[†] Yield = 89%, ee = 98%; confirmed by HPLC analysis of the tosylate **195**.

followed by $Et_3N$ treatment delivered cyclic imine-ester **197** in 81% yield. Hydrogenation of **197** in the presence of $(Boc)_2O$ furnished **198** (78%) along with its C-2 diastereomer (20%). Finally, ester hydrolysis and Boc deprotection afforded (2*S*,3*R*)-3-hydroxy-3-methylproline (**163**).[73]

**Hamada's Synthesis**

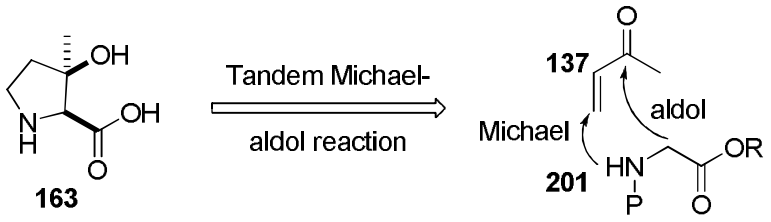
The initial strategy for Hamada's synthesis involved a $SmI_2$ mediated cyclization of the iodoketone **199** (Scheme 1.21). Even though the overall yield for the synthesis was good (ca 28% from (2*S*,3*R*)-threonine), the synthesis was cumbersome (17 steps)[71] and a new strategy to access the material more efficiently was required.

**Scheme 1.20**. $SmI_2$ cyclization approach.



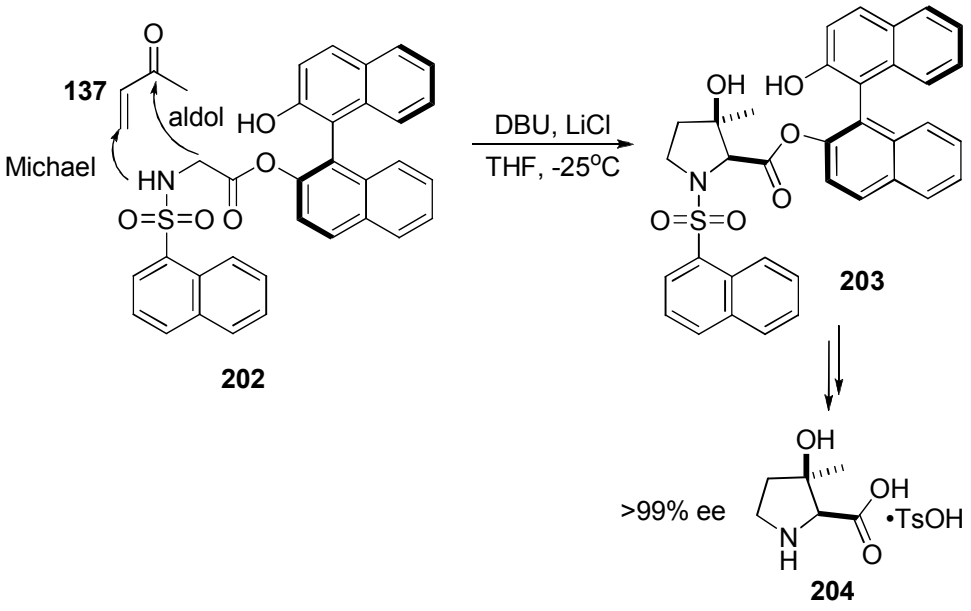

The revised strategy for the synthesis involved a tandem Michael-aldol reaction as shown in Scheme 1.21. Hamada *et al.* successfully reported the synthesis of **163** in both racemic and enantienriched forms.[69, 70]

**Scheme 1.21**. Tandem Michael-aldol approach.



The asymmetric version involved reaction of **202** with MVK (**137**). Toluene sulfonic acid salt **204** was obtained in 39% overall yield from *N*-1-naphthylsulfonyl-glycine via diastereoselective tandem Michael-aldol reaction (Scheme 1.22).[69]

**Scheme 1.22**. Asymmetic version of tandem Michael-aldol approach.

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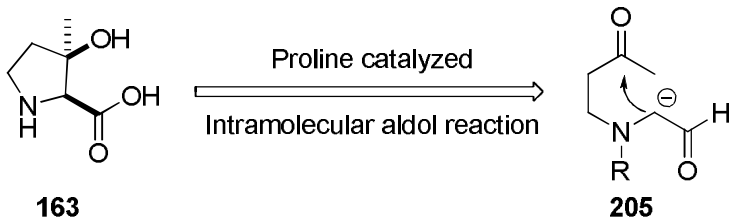
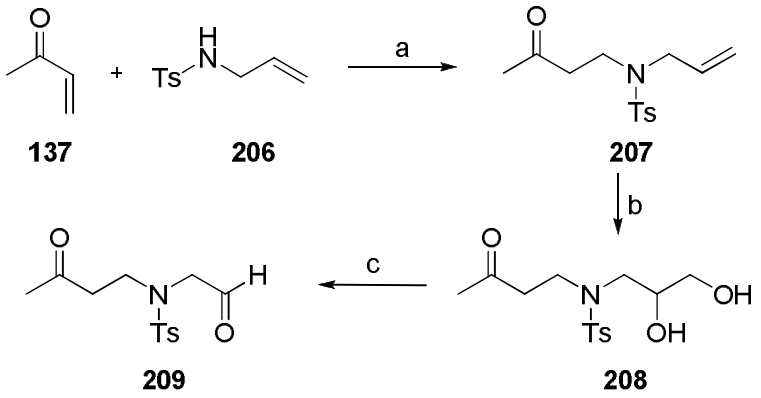
The above method gave proline **163** in good yield and high enantioselectivity but required the use of more than one equivalent of the chiral auxiliary and therefore, a catalytic asymmetric version was highly preferred for an easy access to proline **163**. They envisaged the synthesis of the desired proline fragment by the intramolecular aldol reaction of **205** using proline as catalyst (Scheme 1.23).[67]

**Scheme 1.23**. Organocatalytic strategy of Hamada.



The aldol precursor was synthesized in three linear steps from *N*-tosylallylamide **206**. Michael addition of **206** with MVK followed by dihydroxylation and oxidative cleavage afforded **209** (Scheme 1.24)

**Scheme 1.24**. Synthesis of aldol precursor **209**.




**Reagents and Conditions:** (a) $Na_2CO_3$, *n*-$Bu_4NCl$, $PhCH_3$ (100%); (b) $OsO_4$, NMO, acetone/$H_2O$ (87%); (c) $NaIO_4$, THF (88%).

When the intramolecular aldol reaction of **209** was carried out in $CH_2Cl_2$ or $CH_3CN$ using 30 mol % of proline, racemic diastereomers were observed while enantioenriched **210** was obtained in THF as solvent (dr = 96:4, ee = 62%). Additionally, when 30 mol % of (2*S*,3*R*)-3-hydroxy-3-methylproline (**163**) was used as a catalyst using water as an additive, the enantioselectivity of the desired syn diastereomer **210** was enhanced from 62% to 85%.[†] Investigation of protecting groups on nitrogen showed that the tosyl group was the most appropriate in this particular case to achieve optimum yield and selectivity. The reaction was believed to proceed via a cyclic chair-like transition state to explain the syn selectivity (Figure 1.16).[67]

[†] Using *L*-proline (30 mol %) as catalyst in $CH_2Cl_2$ dr = 64:36 (syn:anti) ee = 1%; in $CH_3CN$ dr = 67:33 (syn:anti), ee = 4%; in THF dr = 95:5 (syn:anti), ee = 49%. Using **163** (30 mol %) in THF dr = 96:4 (syn:anti), ee = 62%. Using **163** (10 mol %) in THF and 5 eq. $H_2O$ dr = 96:4 (syn:anti), ee = 89%. Using **163** (5 mol %) in THF and 5 eq. $H_2O$ dr = 96:4 (syn:anti), ee = 88%.

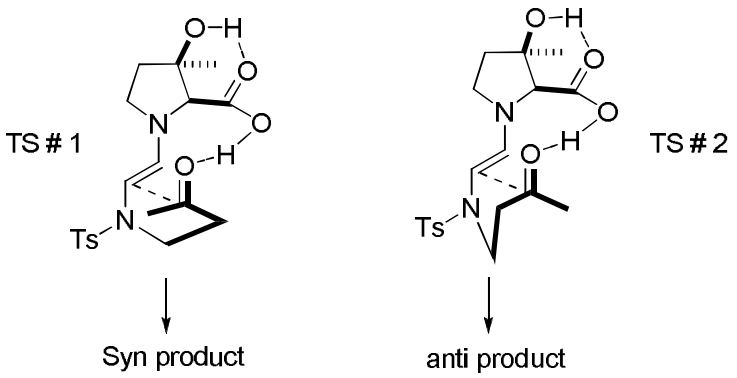
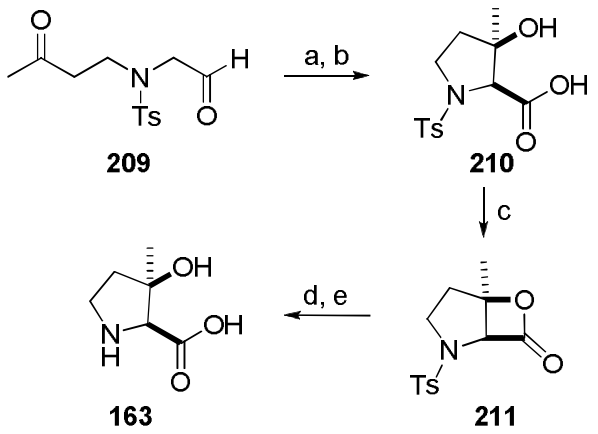



**Figure 1.16**. Possible transition state of the aldol reaction.

**Scheme 1.25**. Completion of the synthesis of **163**.




**Reagents and Conditions:** (a) (2*S*,3*R*)-3-Hydroxy-3-methylproline (**163**), $H_2O$, THF; (b) $NaClO_2$, 2-methyl-2butene, $NaH_2PO_4$, *t*BuOH, $H_2O$; (c) WSCI, DMAP, $CH_2Cl_2$ (66%, 88% ee, 98% ee after one recrystallization); (d) AcCl, MeOH; (e) 6N HCl then Dowex50WX4 (75%)

Intramolecular asymmetric aldol reaction of **209** gave the corresponding aldol adduct **211** after oxidation and lactonization.[†] Lactone **211** was treated with acetyl chloride followed by 6N HCl to access (2*S*,3*R*)-3-hydroxy-3-methylproline (**163**) (Scheme 1.25).[70]

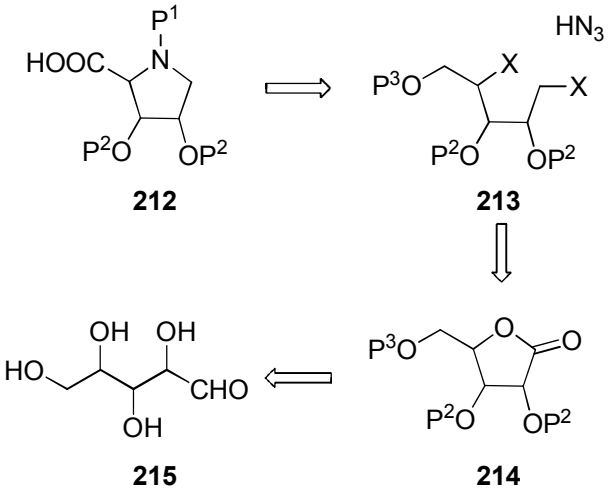
[†] The reaction proceeded with an overall yield of 66% for three steps and 88% ee, which was improved to 98% after one recrystallization.

### 1.3.2.3 Summary of syntheses of (2*S*,3*S*,4*R*)-3,4-dihydroxyproline

**Taylor's Synthesis**

Taylor envisaged the use of a pentose sugar from the "chiral pool" to synthesize all possible isomers of 3,4-dihydroxy proline (Scheme 1.26).[78] They proposed that the proline fragment (**212**) can be synthesized from **213** using a Fleet's double displacement strategy.[79] Intermediate **213** was made by reduction of a suitably chosen γ-lactone **214** which in turn was prepared from the aldopentose **215**.

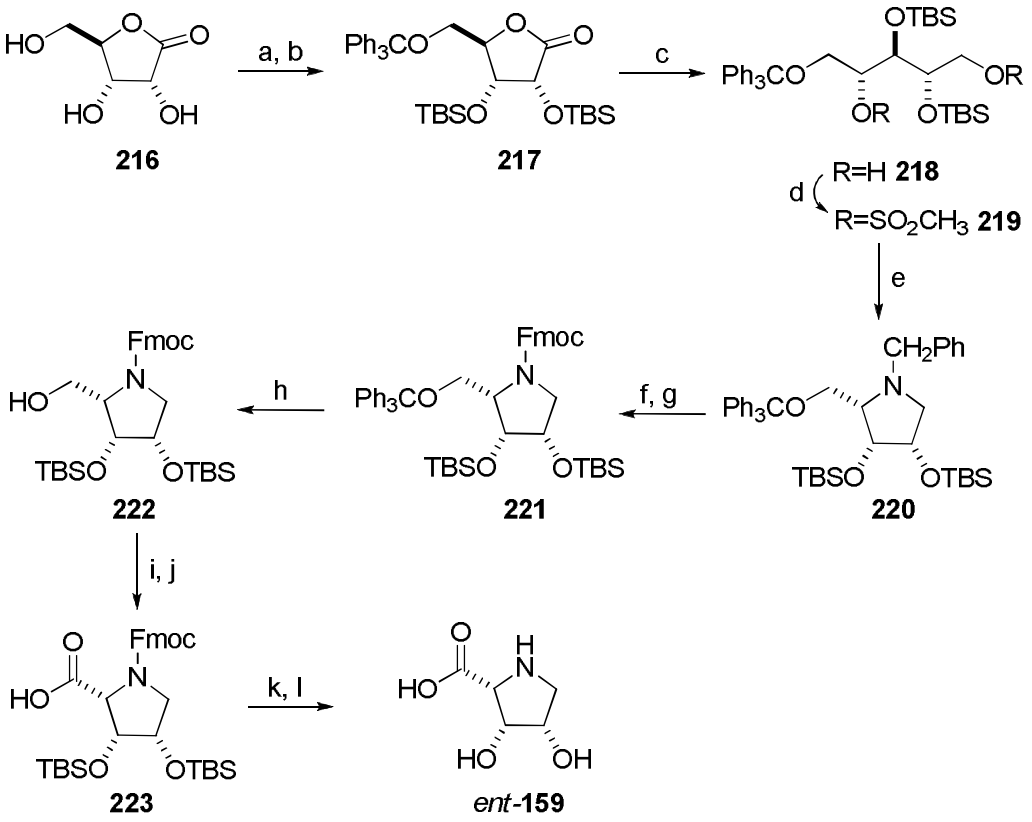
**Scheme 1.26**. Retrosynthetic analysis by Taylor *et al.*




The synthesis began from commercially available D-ribonolactone **216**. The primary alcohol in **216** was selectively protected as its trityl ether followed by TBS protection of the two secondary alcohols to give **217**. Reductive ring opening of lactone **217** was smoothly achieved by $LiBH_4$ to give bis-mesylate **219** after reaction with mesyl chloride. Compound **219** was then subjected to benzyl amine treatment under neat conditions at 80 $^{o}$C for 60 h to give the desired pyrrolidine **220** in 76% yield. The

protecting group on the nitrogen was changed from benzyl to Fmoc and then the trityl ether in **221** was cleaved to give primary alcohol **222**. Swern oxidation of the primary alcohol in **222** followed by $NaClO_2$ oxidation of the resulting aldehyde gave carboxylic acid **223**.[78] Finally, Fmoc deprotection followed by TBAF treatment furnished the desired (2*R*,3*R*,4*S*)-3,4-dihydroxyproline (*ent*-**159**) (Scheme 1.27).[80]

**Scheme 1.27**. Taylor's synthesis of (2*R*,3*R*,4*S*)-3,4-dihydroxyproline.

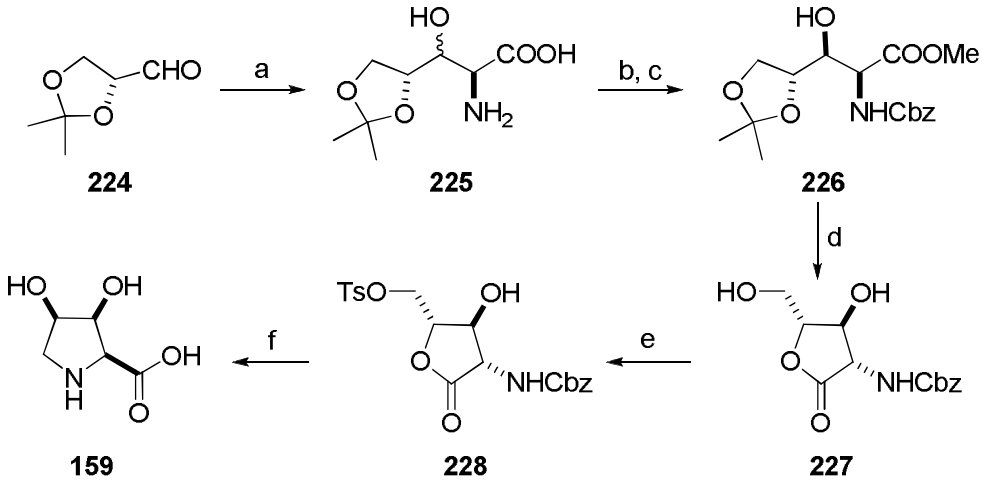



**Reagents and Conditions:** (a) $Ph_3CCl$, py; (b) TBSCl, imidazole, DMF (81% 2 steps); (c) $LiBH_4$, THF (93%); (d) $CH_3SO_2Cl$, py, DMAP (84%); (e) $PhCH_2NH_2$, 80 $^oC$ (76%); (f) $H_2$, Pd/C, EtOH; (g) Fmoc-Cl, $Et_3N$, $PhCH_3$ (75% 2 steps); (h) HCOOH, MeCN (70%); (i) $(COCl)_2$, DMSO, $CH_2Cl_2$, $Et_3N$ (92%); (j) $NaClO_2$, cyclohexene, $KH_2PO_4$ (82%); (k) TFA, $CH_2Cl_2$ then TBAF, THF; (l) Tesser's base (58%).

**Ida's Synthesis**

Ida and co-workers have synthesized (2*S*,3*S*,4*R*)-3,4-dihydroxyproline **159** using L-threonine aldolase (LTA) catalyzed aldol reaction of aldehyde **224** with glycine to give acid **225** in 85% yield (Scheme 1.28).[60] Protection of the amino group in **225** was achieved by reaction with CbzCl while the acid group was protected as its methyl ester giving **226** as the major diastereomer. Deprotection of the acetal in **226** gave the corresponding diol which subsequently underwent lactonization during silica gel purification to give **227** in 73% yield. Tosylation of **227** and Cbz deprotection under acidic conditions furnished the (2*S*,3*S*,4*R*)-3,4-dihydroxyproline (**159**) in 72% yield.

**Scheme 1.28**. Ida's synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyproline.

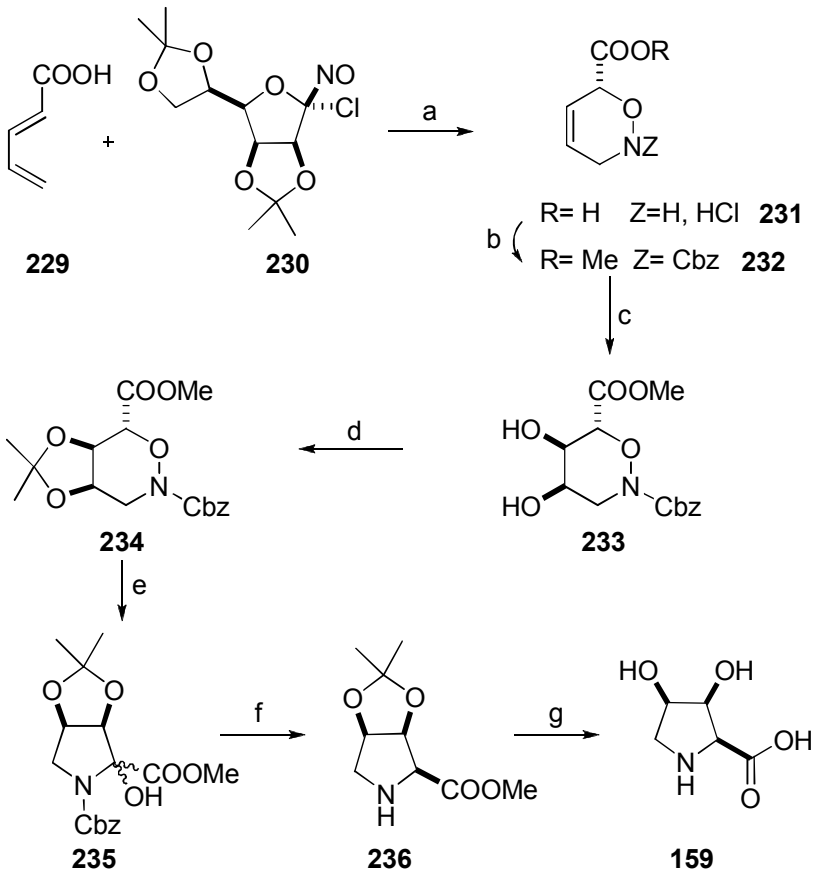



**Reagents and Conditions:** (a) LTA, glycine (85%); (b) CbzCl (70%); (c) $Cs_2CO_3$, MeI (93%); (d) $I_2$, MeOH (78%); (e) TsCl, Py (75%); (f) $H_2$, HCl, Pd/C, $Ba(OH)_2$, dioxane, $H_2O$ (72%).

**Defoin's Synthesis**

Defoin's synthesis of **159** started via a Diels-Alder reaction of diene **229** with chiral chloro-nitroso derivative (**230**) to access the hydrochloride salt **231** (Scheme 1.29).[81] Cbz protection of the amino group furnished **232** in 86% ee.[†] Dihydroxylation of **232** gave **233** as a major diastereomer (dr 82:18). Acetonide formation followed by rearrangement using $Na_2CO_3$ gave hemi-aminal **235** as a 75:25 mixture of diastereomers.

**Scheme 1.29**. Defoin's synthesis of (2*S*,3*R*,4*S*)-3,4-dihydroxyproline.




**Reagents and Conditions:** (a) $CH_2Cl_2$, EtOH (75%); (b) $ClCO_2Bn$, $NaHCO_3$ then HCl, MeOH (86% ee, 95% ee after recrystallization); (c) $OsO_4$, NMO, acetone/$H_2O$ (69% dr = 82:18); (d) 2,2-dimethoxypropane, amberlyst 15, (100%); (e) $Na_2CO_3$, MeOH; (f) Pd/C, MeOH; (g) aq. 6N HCl 50 $^oC$ (94%).

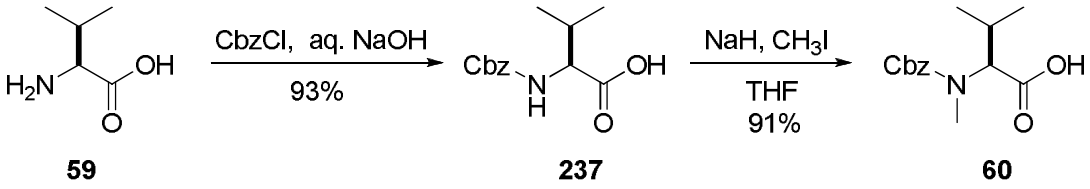
[†] ee was improved to 95% after one recrystallization.

Finally, hydogenolysis, acetonide deprotection and ester hydrolysis gave (2*S*,3*S*,4*R*)-3,4-dihydroxyproline (**159**) in good yield.[81]

### 1.3.3 *N*-Methyl-L-valine

The preparation of *N*-methyl-L-valine (**60**) is well-known (Scheme 1.30). Protection of L-valine (**59**) with CbzCl gives **237**[82] which upon reaction with MeI in the presence of NaH affords **60**.[83]

**Scheme 1.30**. Synthesis of Cbz-*N*-Me-Val (**60**).

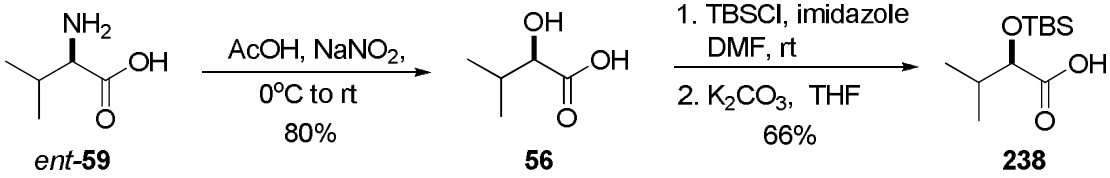



**59** **237** **60**

### 1.3.4 (2*R*)-2-hydroxy-3-methylbutanoic acid

Reaction of D-valine (*ent*-**59**) with sodium nitrite/AcOH proceeds smoothly with retention of configuration to hydroxy acid **56**.[84, 85] Next, TBS protection of acid **56** followed by hydrolysis furnishes hydroxy acid **238**[86] (Scheme 1.31).

**Scheme 1.31**. Synthesis of **238**.




*ent*-**59** **56** **238**

## 1.4 Basic concepts in depsipeptide synthesis

Approaches towards the syntheses of sesquiterpene and proline fragments related to those present in depsilairdin (**55**) have been elaborated above. En route to the total synthesis of **55**, a crucial ester coupling of lairdinol A (**51**) and the sterically hindered proline carboxylic acid group without substantial decomposition or isomerization is one of the major challenges in the planned total synthesis. A brief account of selected literature examples for esterification of sterically hindered reactants is presented below. In addition, literature methods/tactics used to couple sterically hindered amino acids are also briefly discussed.

### 1.4.1 Protection, activation and coupling of amino acids

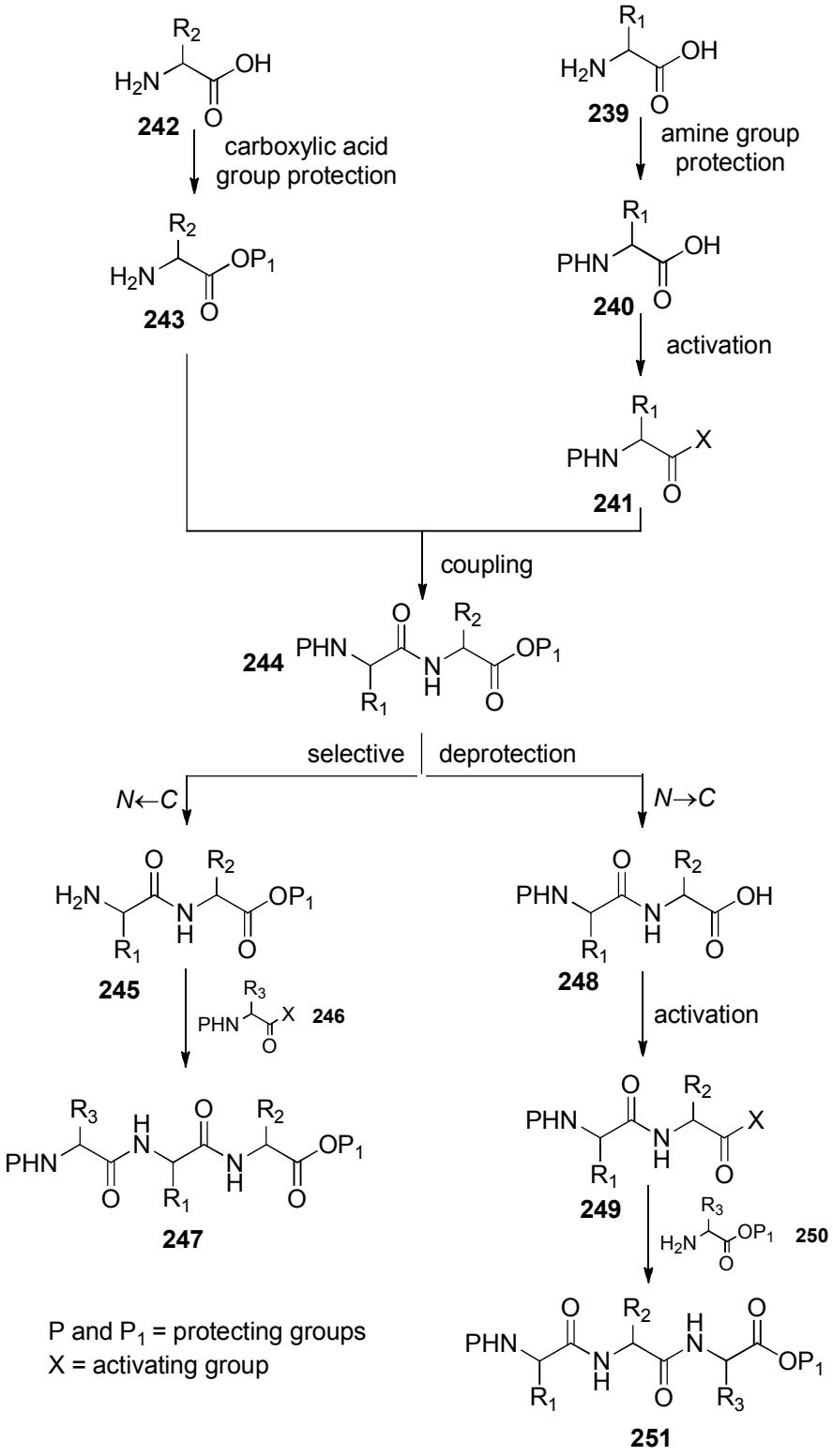
Depsipeptide natural products have both amide and ester linkages. The synthesis of amides from amino acids has been exhaustively studied. When two amino acids are mixed with each other at room temperature, they form a salt, but at a higher temperature, a peptide bond results. Generally, such harsh conditions are not applicable for the synthesis of (depsi)peptides. The most common synthetic approach for generating an amide linkage between amino acids involves reaction of an *N*-protected (e.g. as amide or carbamate) amino acid with a *C*-protected (e.g. as an ester or amide) amino acid. Common protecting groups for the carboxylic acid group in amino acids are benzyl, *t*-butyl and methyl esters while *t*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethoxycarbonyl (Fmoc) carbamates are commonly used for protecting the amino group. This approach avoids the potential oligomerization that could result if these

functional groups were unprotected. Amide formation requires activation of the carboxylic acid moiety, for example by employing its anhydride,[87] acyl azides[88] or various other activated ester derivatives[88] (Figure 1.19, *vide infra*). Activation of the carboxylic acid can be done in a separate step or in situ in the presence of the amine coupling partner.

### 1.4.2 Strategies for chain extension in peptide synthesis

Two general strategies to extend peptide chain are known; (i) *N*-terminal extension (*N*←*C*; sequential acylation of the *N*-terminal residue) and (ii) *C*-terminal extension (*N*→*C*; sequential amidation of the *C*-terminal residue) (Scheme 1.32).[89] In the *N*→*C* strategy, deprotection of the terminal carboxylic acid group is required at every coupling stage, followed by activation and then coupling with the next C-protected amino acid while the *N*←*C* strategy requires deprotection of the terminal amino group followed by coupling with the next amino acid (*N*-protected and carboxylic acid activated). Nature builds up peptides via an *N*→*C* approach but the *N*←*C* protocol is generally preferred in laboratory synthesis because it is less susceptible to epimerization when dealing with labile substrates.

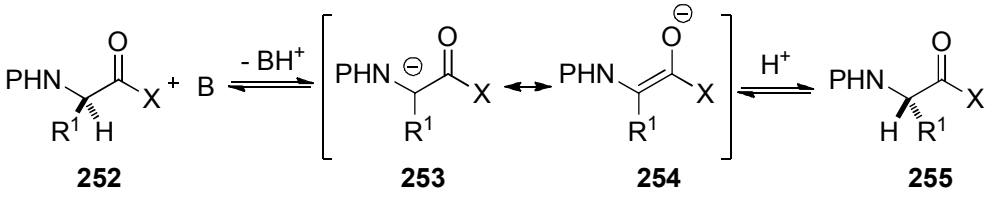
**Scheme 1.32.** Peptide bond formation and strategies for peptide chain extension.



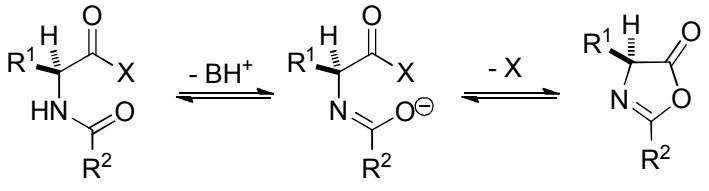
### 1.4.3 Side reactions in peptide synthesis

During the carboxylic acid activation process, the reactive species that is formed (e.g. acid chloride) can undergo various side reactions. Racemization, or more commonly epimerization, generally occurs during the activation or the coupling steps. To avoid this inherent drawback, an understanding of the mechanism is crucial. Racemization occurring in the presence of bases and via azalactones [5(4*H*)-oxazolone][90-92] formation have been proposed (Figure 1.17). In activated species **252**, the α-H has enhanced acidity due to the presence of an electronegative group (X) and is prone to base abstraction leading to stabilized carbanion **253**/enolate (**254**), which can then be protonated from either face giving two stereoisomers (**252, 255**).

i) Base catalyzed epimerization




ii) Isomerization via 5(4*H*)-oxazolone




X = Electronegative group

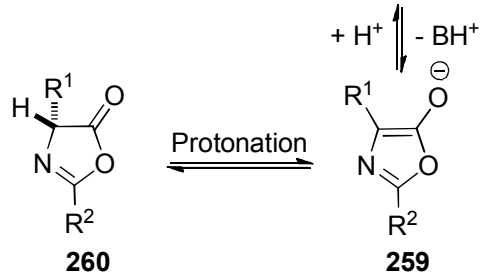
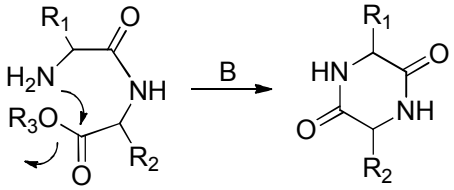



**Figure 1.17**. Proposed mechanisms for isomerization during peptide synthesis.

Alternatively, the presence of X as a good leaving group promotes formation of the oxazolone **258** (Figure 1.17). The propensity for racemization via the oxazolone formation can be rationalized by the formation of the resonance stabilized carbanion **259**. These stabilized aromatic intermediates can be protonated from either face to give a mixture of isomers. The *N*←*C* chain extension strategy is generally preferred due to the lower tendency of racemization, at least via the oxazolone route. This is attributed to the lower tendency for oxazolone formation by carbamates compared to amides.




**261** **262**

**Figure 1.18**. Diketopiperazine formation during peptide synthesis.

Diketopiperazine formation is another important side reaction in the peptide synthesis particularly in the coupling of the third residue in a *N*←*C* approach. In the presence of base, the free amino group of a dipeptide ester can easily undergo cyclization to form the diketopiperazine (**262**) (Figure 1.18). Generally, bulky ester groups (e.g. *t*-butyl) and Boc-hydrazide derivatives are used to suppress this reaction.[89, 93]

### 1.4.4 Coupling methods and coupling reagents

Acid chlorides have been traditionally used to form peptide bonds when coupling simple molecules. Because of the harsh conditions employed to prepare acid chlorides (e.g. $SOCl_2$) and concurrent side reactions,[89] several other methods had been invented.

Curtius introduced the use of acyl azides in peptide synthesis which are reported to suppress side reactions (e.g. DKP formation).[93] Acid anhydrides have also been utilized in the peptide coupling; good selectivities are seen if the relative steric hindrance and/or reactivities of the two carbonyls present in anhydrides are adjusted appropriately. Format-

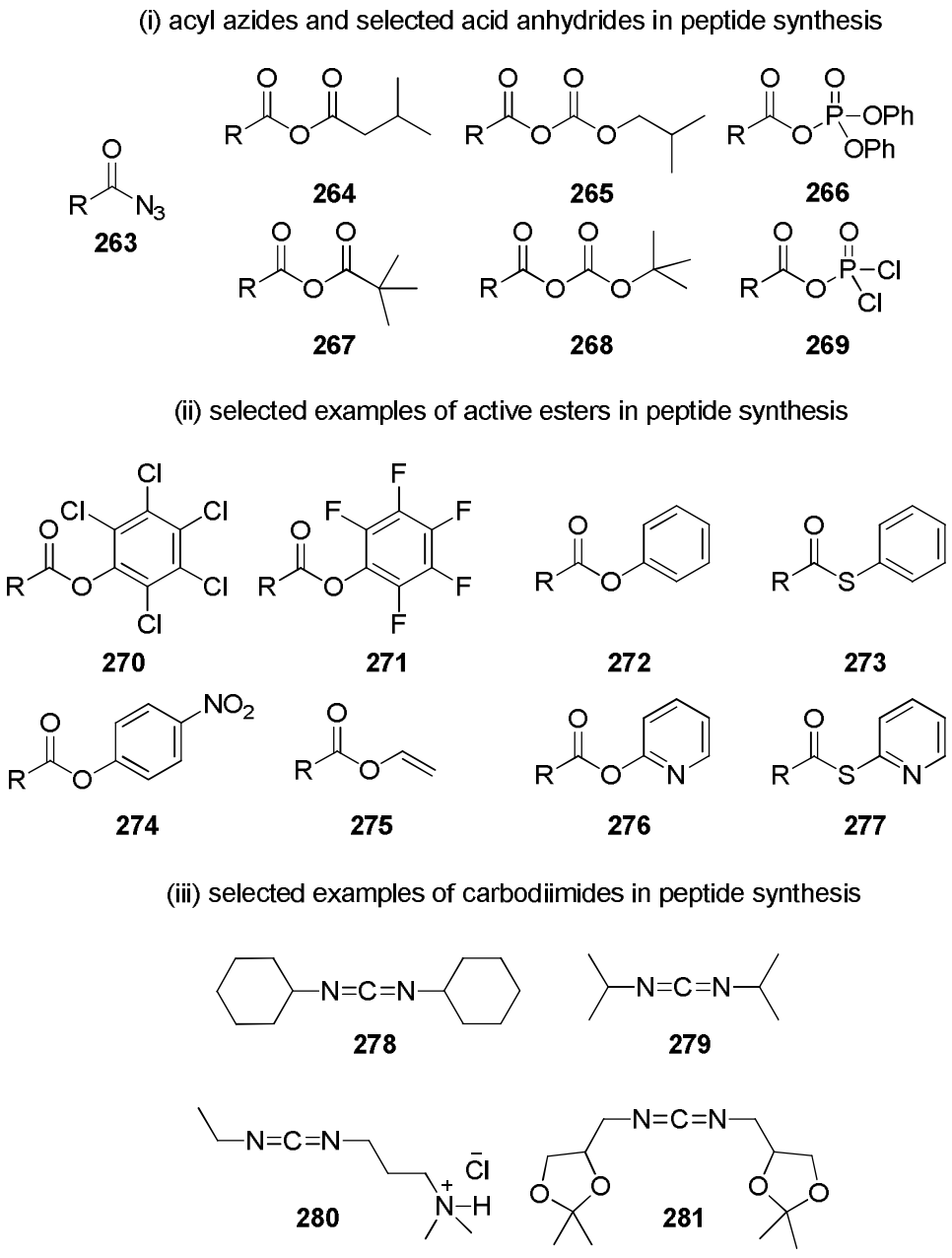
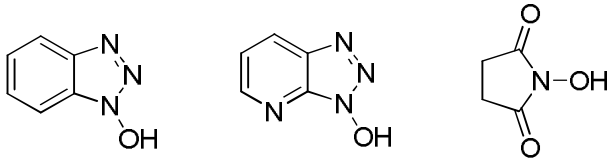



**Figure 1.19**. Anhydrides, active ester and carbodiimides in peptide synthesis.

-ion of undesired products arising from the use of anhydrides can be potentially reduced or eliminated by the introduction of active esters (Figure 1.19). The reactivity of the carbonyl group can be varied greatly by changing the active group, thus affording selective coupling.

Carbodiimides are a class of commonly used coupling reagents that involve the *in situ* activation of the carboxylic acid in the presence of the amine component to form a peptide bond. *N,N'*-Dicyclohexylcarbodiimide[94] (DCC, **278**) is one the most commonly utilized diimides for peptide (ester) couplings, regardless of the extent of accompanying side reactions[95] (isomerization, *O-N* acyl transfer). The dicyclohexylurea formed during the DCC mediated coupling reaction can be difficult to remove using standard work-up methods. Carbodiimides such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride[96, 97] (EDCI·HCl, **280**) and bis[4-(2,2-dimethyl-1-3dioxolyl)]methyl carbodiimide[98] (BDDC, **281**) that are water soluble have been designed to facilitate removal of the urea by-products upon aqueous work-up (Figure 1.19).

A number of coupling additives such as 1-hydroxybenzotriazole[99] (HOBt, **282**), 1-hydroxy-7-azabenzotriazole[100] (HOAt, **283**) and *N*-hydroxysuccinimide[101] (HONSu, **284**) have been designed and successfully applied to reduce isomerization when DCC or related carbodiimides are employed as peptide coupling agents (Figure 1.20). Coupling additives (HOBt or HOAt) react with the *O*-acylurea intermediate (**288**, Scheme 1.33) to

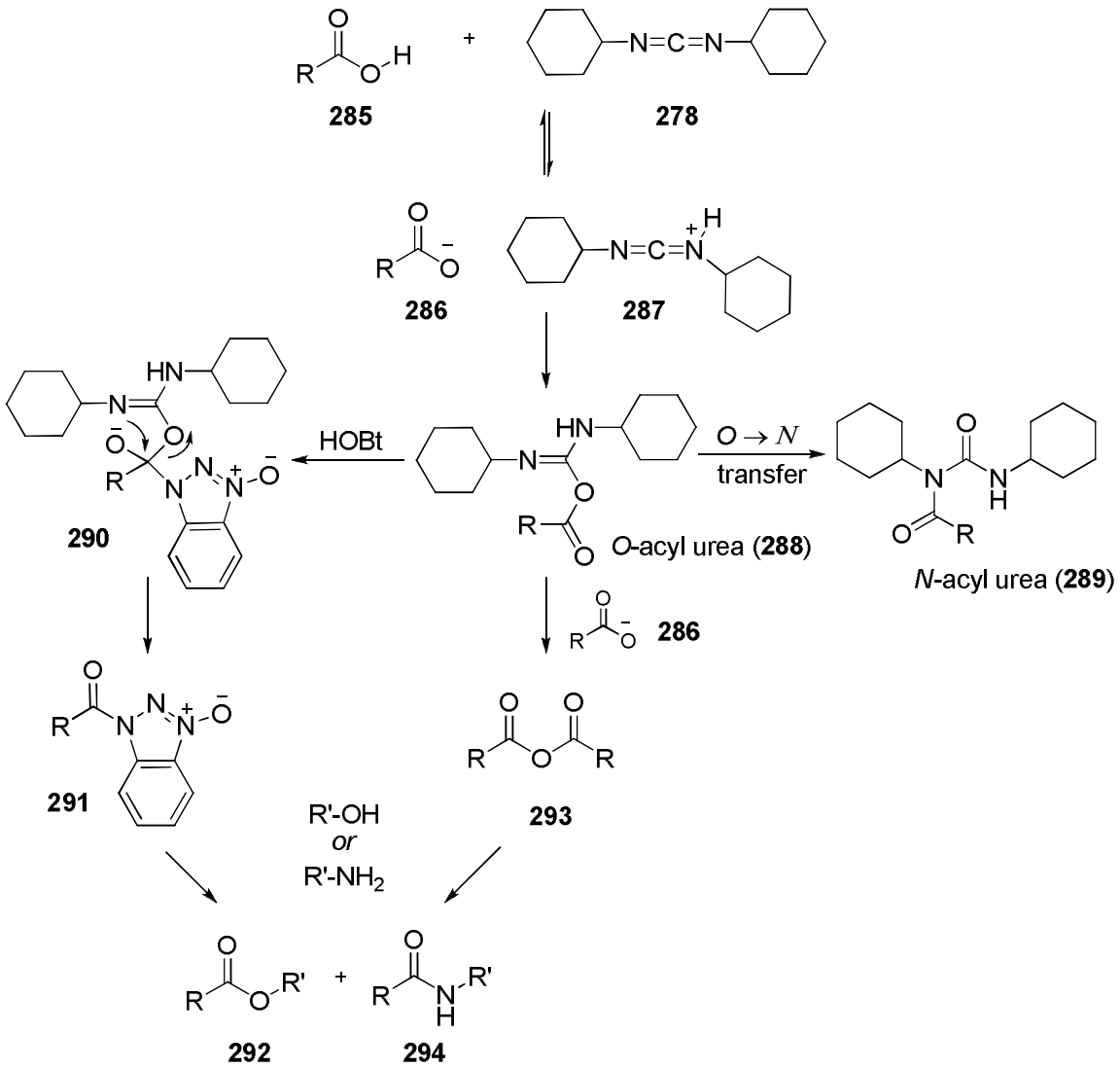



**282** **283** **284**

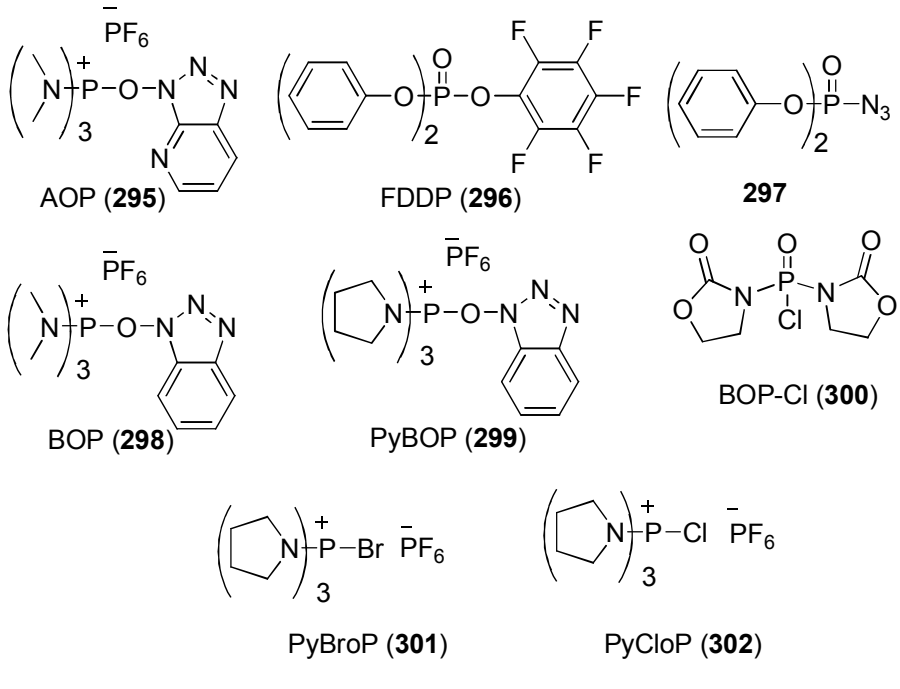
**Figure 1.20**. Coupling additives.

produce a less reactive ester which reduces the risk of epimerization. A proposed mechanism for DCC mediated amide formation is shown in Scheme 1.33.

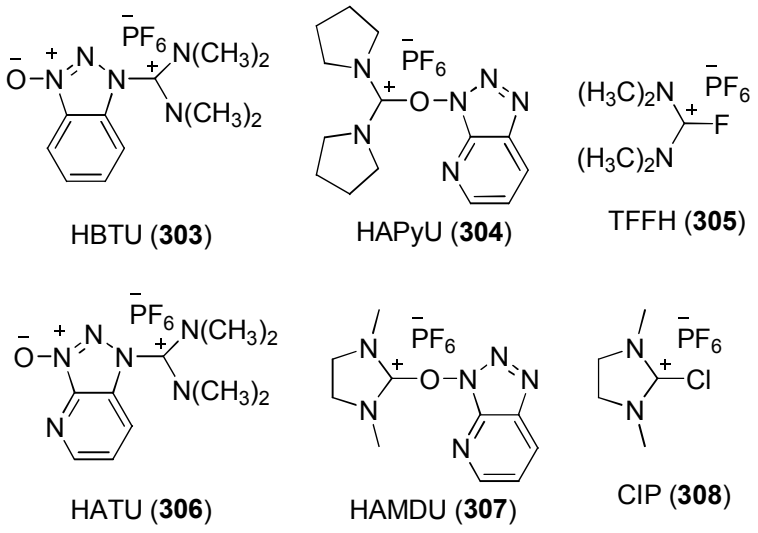
**Scheme 1.33**. Proposed mechanism for coupling reaction using DCC.



Several phosphorous and uronium based coupling reagents[102] have been prepared and studied for the coupling of sterically hindered substrates where DCC, EDCI or BDDC provided unsatisfactory outcomes. The extent of epimerization was also found to be minimized when engaging these reagents (Figure 1.21).




(i) Selected phosphorous based coupling reagents




(ii) Selected uronium based coupling reagents

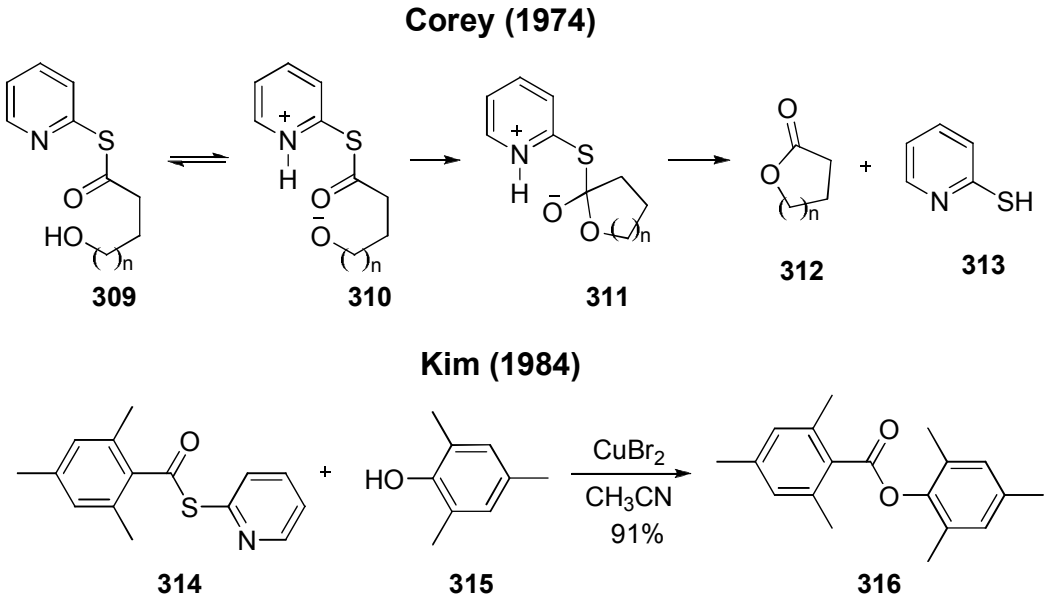
**Figure 1.21**. Selected phosphorous based and uronium based coupling reagents.

## 1.5 Methods of esterification

Esters are generally prepared by reacting a carboxylic acid and an alcohol under refluxing or ambient acidic conditions. Less harsh methods involve the use of acid chlorides and/or anhydrides as tactics to activate the carboxylic acid for ester formation. Yamaguchi has developed an esterification method by reacting the carboxylic acid with 2,4,6-trichlorobenzoyl chloride to make its anhydride followed by reaction with the alcohol to generate the ester bond.[103] However, this method has been mostly utilized in the context of macrolactonization. Although Yamaguchi protocol is robust, when hindered alcohols are used, mixtures of products are seen. Reaction of acid chlorides with alkoxides is not a general protocol due to side reactions caused in the presence of strong basic mediums.[104] Surprisingly, only a few methods involving esterification of hindered alcohols or carboxylic acids have been developed to date.

In search of new methods to form sterically hindered esters, various activating groups have been developed (Figure 1.19), and it was found that thiopyridyl ester enjoyed the greatest success of all screened. Corey successfully used thiopyridyl esters to form lactones **312** under refluxing conditions in toluene (Scheme 1.34).[105] However, the required high temperatures are not suitable for sensitive substrates and Corey's method cannot be generalized.

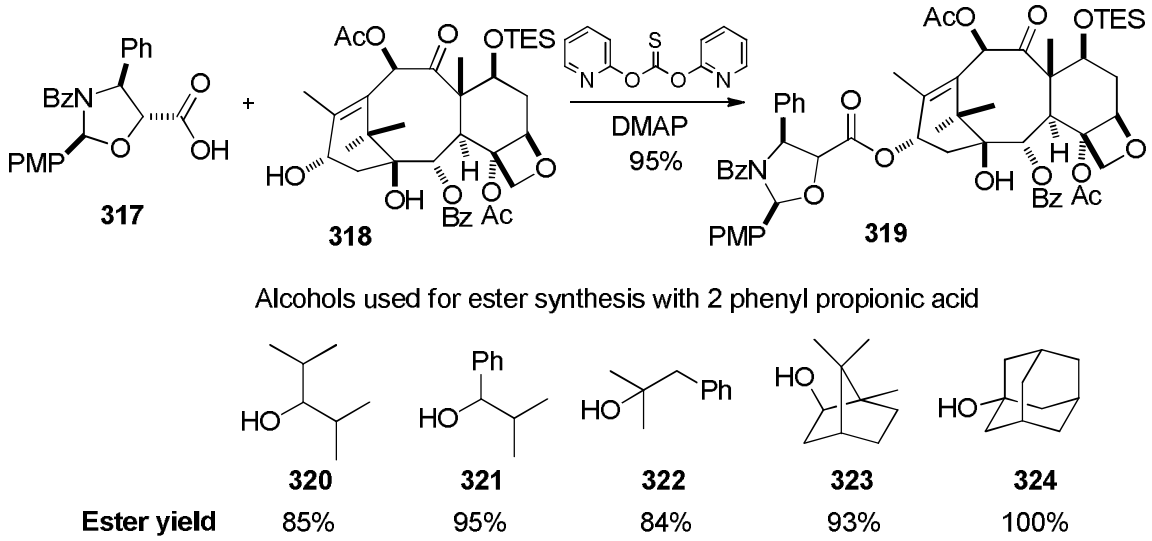
**Scheme 1.34**. Use of thiopyridyl esters in lactonization/esterification.




Kim and co-workers utilized thiopyridyl esters to synthesize sterically hindered esters using $CuBr_2$ to promote the coupling process (Scheme 1.34). [106] The reaction is proposed to proceed via the formation of an acid bromide intermediate. Again, the reaction conditions are harsh for sensitive substrates due to the strong Lewis acidity of $CuBr_2$. Kim has also realized the synthesis of esters using lithium dialkylcuprates and pyridyl thioesters in the presence of oxygen.[107]

Mukaiyama has made use of *O*,*O*'-di(2-pyridyl)thiocarbonate (DPTC) and DMAP for the synthesis of sterically demanding esters (Scheme 1.35).[108] This method has been utilized in the synthesis of taxol and various other sterically hindered esters have been prepared successfully.

**Scheme 1.35.** Mukaiyama's ester synthesis.

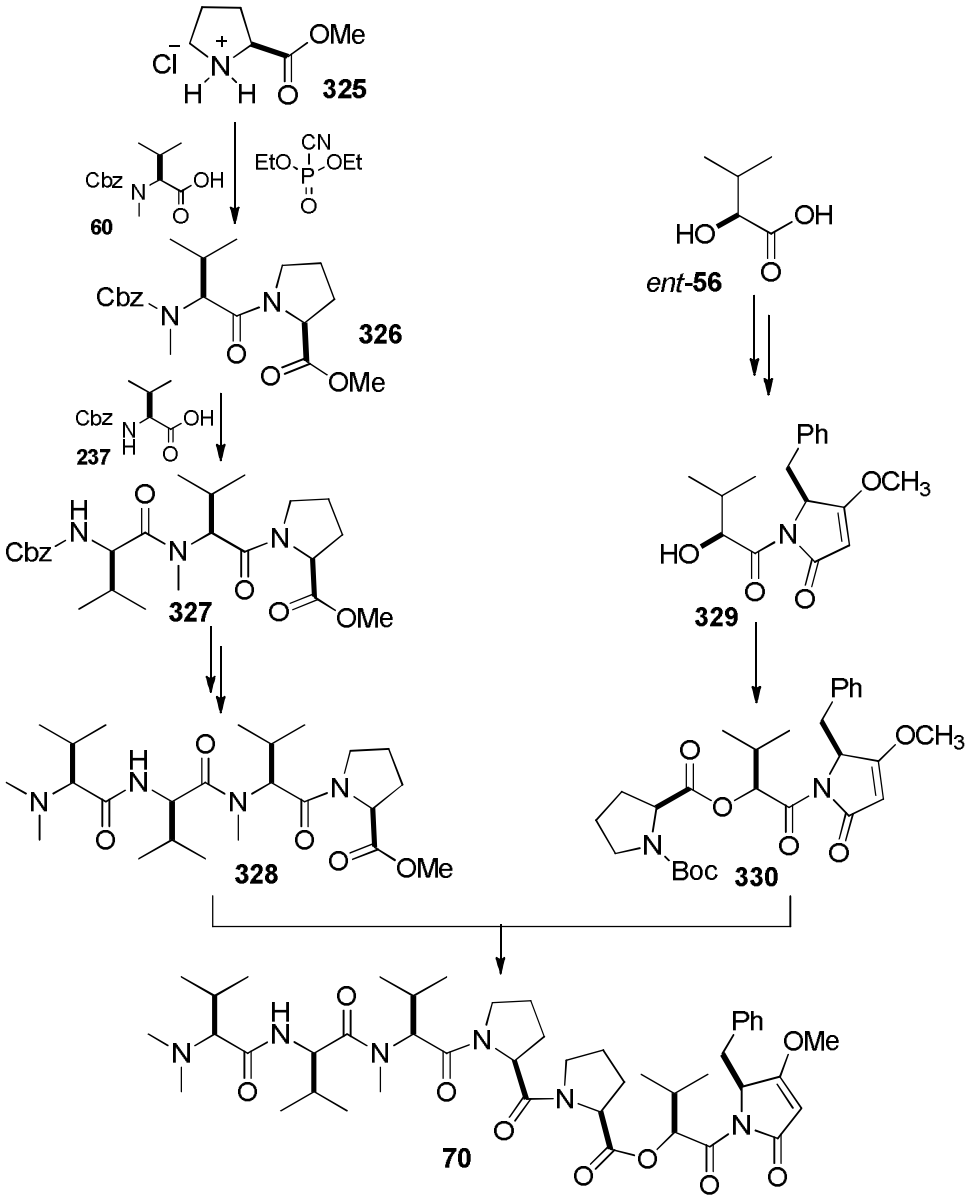



## 1.6 Synthesis of natural products containing hindered peptide and ester bonds

### 1.6.1 Synthesis of dolastatin 15

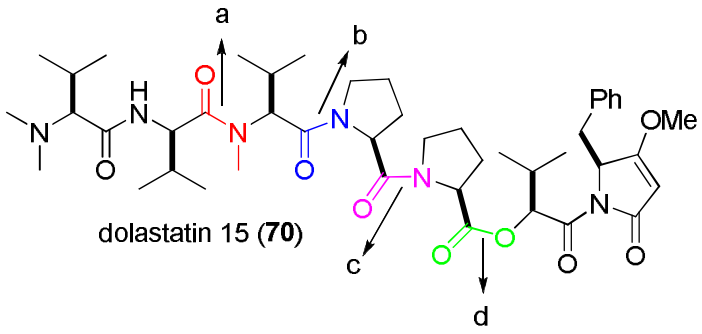
The synthesis of dolastatin 15 (**70**) is an excellent example where difficult amide and ester linkages have been constructed from sterically demanding substrates. Pettit utilized diethylphosphonocyanidate (DEPC) to couple **325** with **60** (77% yield). While the new peptide bond in **327** was tailored via pivaloyl mixed anhydride (83% yield), esterification of alcohol **329** was carried out using DCC and 4-pyrrolidinopyridine with 74% yield. The synthesis of dolastatin 15 (**70**) was completed by coupling **328** and **330** after deprotection using DEPC in 68% yield (Scheme 1.36).[109]

**Scheme 1.36.** Synthesis of Dolastatin 15 (**70**).




Coste[110] and Akaji[111] have also synthesized dolastatin 15 (**70**) (See Table 1.4 for details about the amide and the ester bonds formation).

**Table 1.4**. Synthesis of key bonds in dolastatin 15 (**70**).




| | By Pettit *et al.*[a] | | By Coste *et al.*[b] | | By Akaji *et al.*[c] | |
|---|---|---|---|---|---|---|
| **Bond** | **Reagent** | **Yield** | **Reagent** | **Yield** | **Reagent** | **Yield** |
| a | $(CH_3)_3CCOCl$, NMM | 83% | PyCloP, DIEA | 95% | CIP, DIEA, HOAt | |
| b | DEPC, $Et_3N$, | 77% | PyCloP, DIEA | 83% | CIP, DIEA, HOAt | |
| c | DEPC, $Et_3N$ | 68% | PyCloP, DIEA | 85% | CIP, DIEA, HOAt | 84% |
| d | DCC, 4-pyrrolidino-pyridine | 74% | IPCC, $Et_3N$, DMAP | 76% | CIP, DMAP | 92% |

[a]Ref. 109, [b]Ref. 110, [c]Ref. 111.

Other examples of synthetic targets containing hindered peptide and ester bonds such as apratoxin A (**331**) synthesized by Chen and Forsyth,[112] aurilide (**332**) synthesized by Yamada *et al.*,[113, 114] and destruxin B (**333**) synthesized by Ward *et al.*[115] are shown in Figure 1.22.

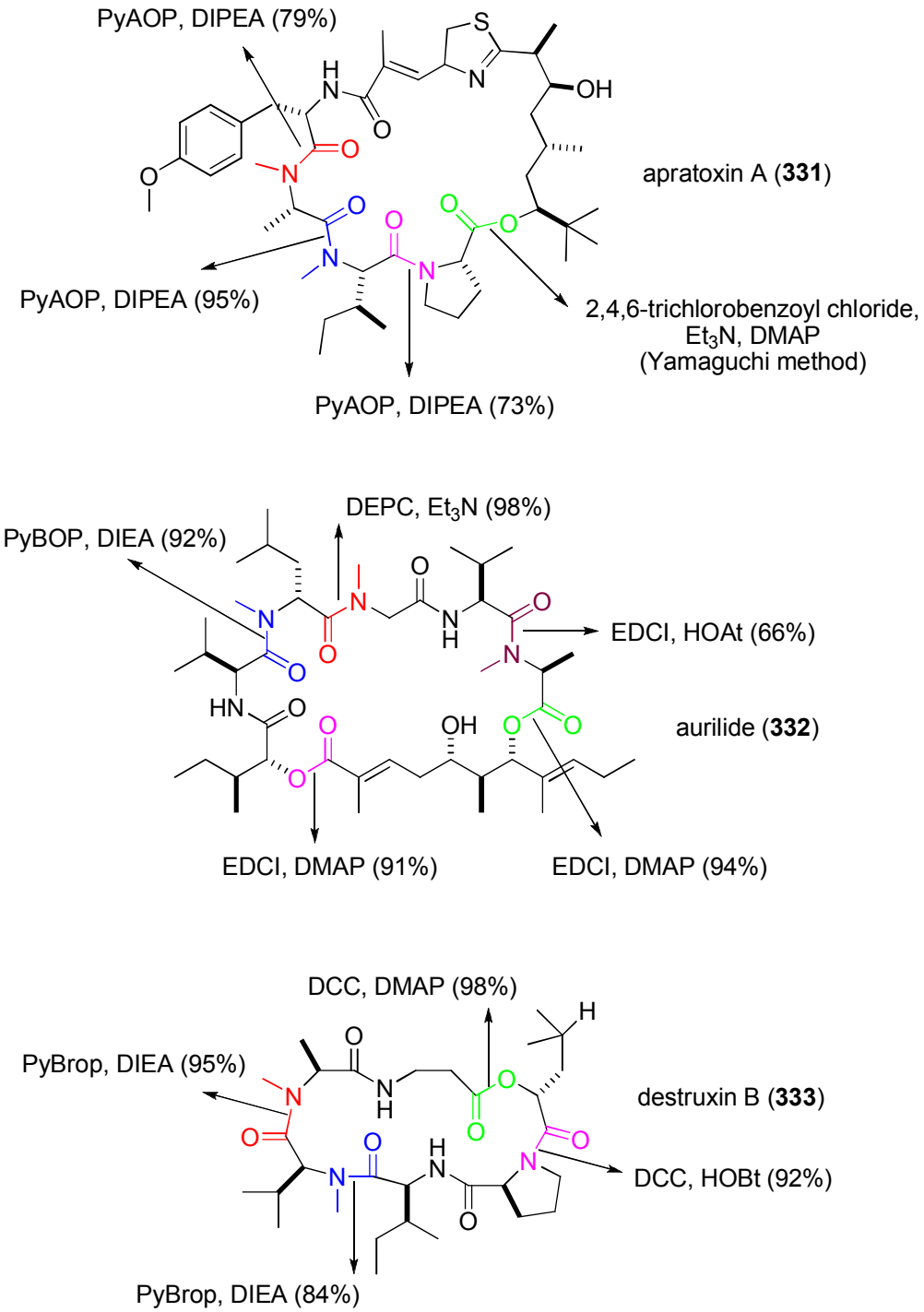



**Figure 1.22**. Synthesis of key bonds in apratoxin, aurilide and destruxin B.

## 1.7 Summary

Blackleg is a fungal disease that has caused severe damage to canola crops in Canada and worldwide. A number of methods such as crop rotation, sanitation, burning or burying the infected crop residues, development of blackleg resistant species and fungicides help control the disease to a great extent. Despite these available measures, an efficient mode of treatment is still required. Extensive research is being conducted to comprehend the chemical interactions between plants and their pathogens. As part of an active research program in this discipline, the Pedras group has isolated depsilairdin (**55**), a new host selective phytotoxin that could be a potential probe to aid the design of new agents to treat blackleg and other devastating diseases in the agricultural sector. Depsilairdin was found to be highly selective towards brown mustard, forming strong necrotic and chlorotic lesions while other mustard plants such as canola and white mustard were unaffected. The phytotoxicity of **55** mimics the pathogen as it causes symptoms in brown mustard, similar to those caused by the fungus. It is very important to study the mechanism of action of **55** on plants. Depsilairdin was isolated in minute quantities from Nature; its total synthesis is required in order to access sufficient quantities to unveil its biological secrets. It is an acyclic depsipeptide which contains residues of (2*R*)-2-hydroxy-3-methylbutanoic acid (Hmb, **56**), *N*-methyl-L-valine (*N*-Me-Val, **57**), a novel proline derivative [(2*S*,3*S*,4*S*)-3,4-dihydroxy-3-methylproline, **58**] and the sesquiterpene fragment lairdinol A (**51**) (Figure 1.6). The residues **56** and **57** are well-known and readily available from D- and L-valine, respectively. However, **51** and **58** are novel compounds that have not been synthesized previously. Thus, the objective

of my research was to develop efficient syntheses of **57** and **58** and effect a total synthesis of depsilairdin by coupling the five residues.

# 2 Results and discussion

## 2.1 Objectives

Depsilairdin (**55**) is a host-selective phytotoxin consisting of five residues; a novel sesquiterpene fragment, lairdinol A (**51**); the previously unknown amino acid (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline (**58**); two *N*-methyl-L-valine residues (**57**) and (2*R*)-2-hydroxy-3-methylbutanoic acid (**56**) (Figure 2.1). Depsilairdin (**55**) was found to have highly selective toxicity towards brown mustard causing strong necrotic and chlorotic lesions while other mustard plants such as white mustard and canola remained unaffected even at relatively high concentrations ($10^{-3}$ M).[25] The phytotoxicity of **55** mimics the pathogen as it causes symptoms in brown mustard similar to those caused by the fungus. Understanding the mode of action of **55** in plants can very possibly provide a strong lead to develop new chemical measures against blackleg disease. However, this current task is tedious due to low quantities of depsilairdin (**55**) isolated from Nature. The aim of this research was to develop a synthesis of **55** that could provide useful amounts for biological evaluations.

There are no previous syntheses of fragments **51** and **58**; however, residues **56** and **57** can be easily prepared from D-valine and L-valine, respectively. The objectives of the current research were to synthesize fragments **51** and **58** in an efficient manner followed by coupling of the five fragments to enable the total synthesis of depsilairdin (**55**). Studying the biological activities of **55** along with analogues prepared using alternative proline derivatives (e.g., L-proline, *cis*-4-hydroxy-L-proline, *trans*-4-dihyroxy-L-proline, etc.) was also considered. Thus, the syntheses of various depsilairdin analogues were also undertaken.

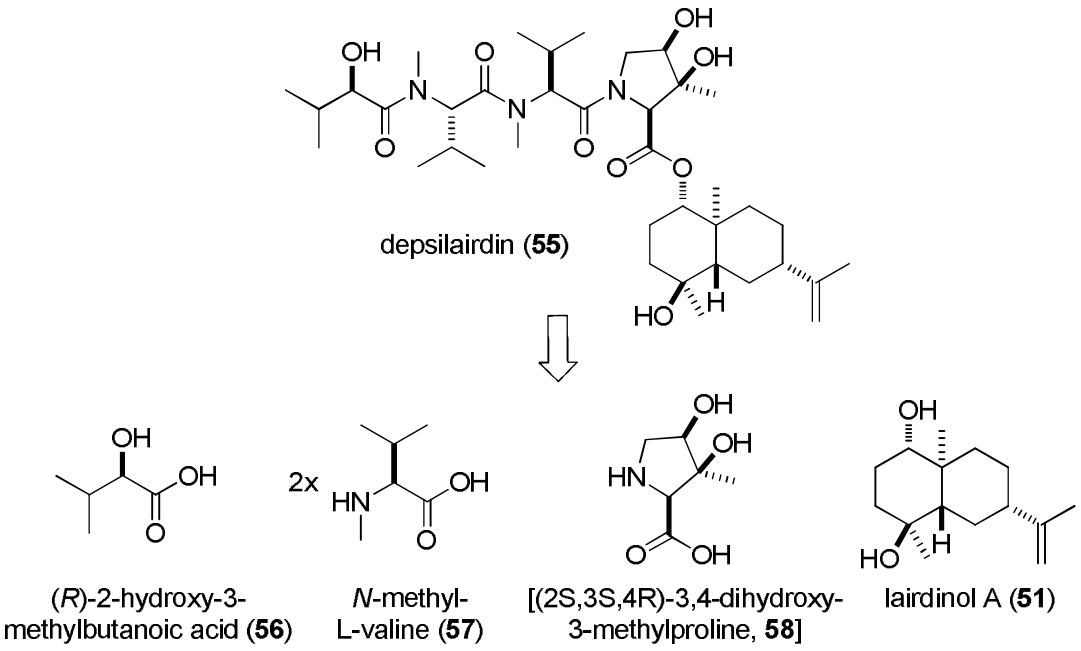



**Figure 2.1**. Structure of depsilairdin (**55**) and its component residues.

## 2.2 Synthesis of depsilairdin

### 2.2.1 Retrosynthetic analysis

In principle, depsilairdin (**55**) can be dissected into five fragments (**51**, **60**, **337** and **338**) as shown in Scheme 2.1. The assembly of these fragments in the correct sequence is crucial in order to avoid failure at the coupling stage (e.g., caused by either steric, conformational, or electronic effects) and isomerization of labile fragments. Depsilairdin has three peptide bonds which can be generated either via an *N*-terminal extension (*N*←*C*) or a *C*-terminal extension (*N*→*C*) approach. The *N*-terminal extension is the preferred strategy as it offers a lower tendency for racemization (see section 1.4.2). A retrosynthetic analysis for depsilairdin in this regard is shown in Scheme 2.1.

The key points of the disconnections are;

(a) Disconnection of the ester linkage provides the eudesmane sesquiterpene fragment, lairdinol A (**51**), and a tetrapeptide acid **335**. Esterification of **335** by *C*-terminal extension of the proline fragment should be feasible as proline is resistant to isomerization.

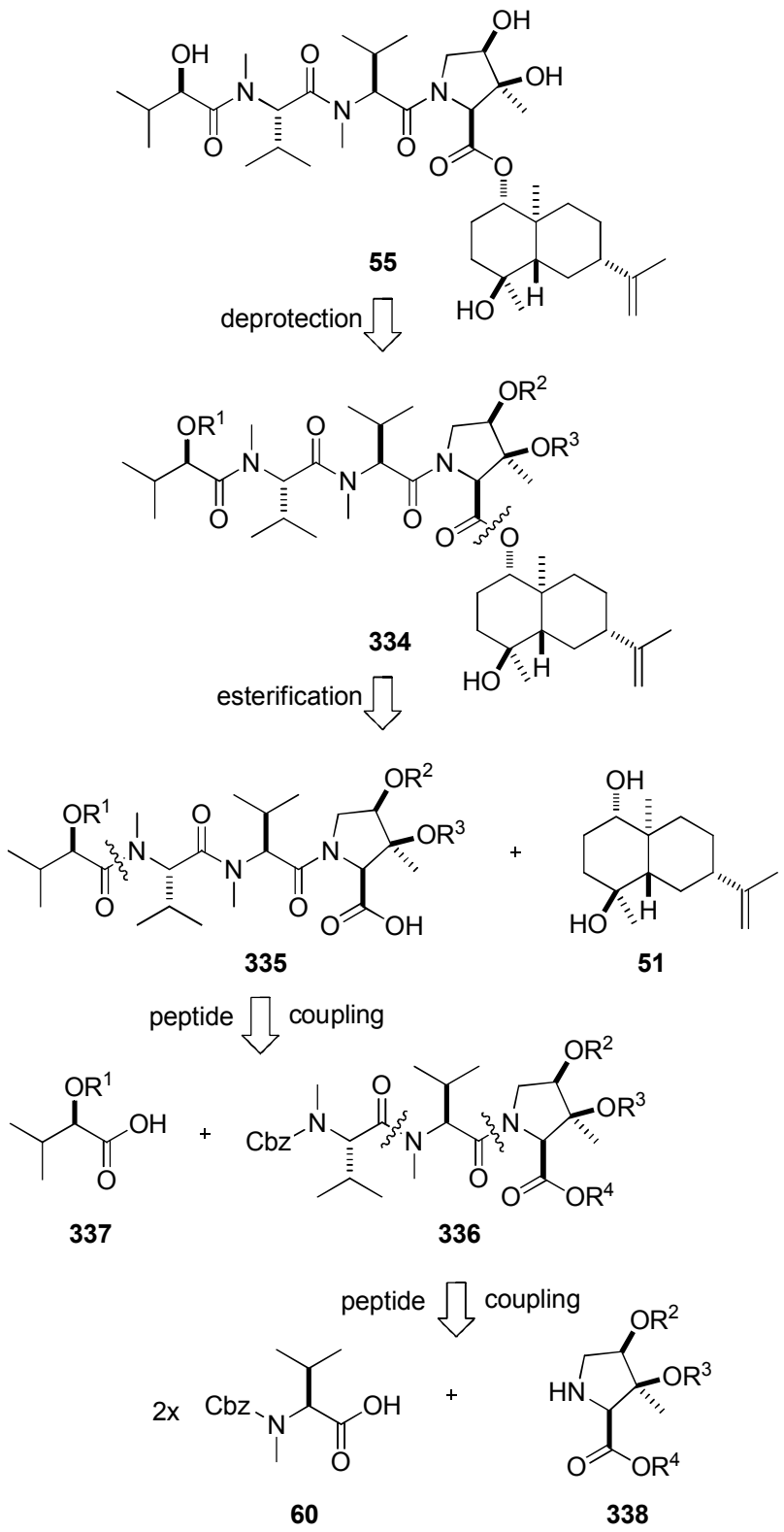
(b) Tetrapeptide **335** can in turn be derived from hydroxy acid **337** and suitably protected tripeptide fragment **336** (amide bond disconnection).

(c) Tripeptide **336** can be derived from protected dihydroxyproline **338** and two *N*-methyl-L-valine fragments **60** (amide bond disconnection).

The choice of the protecting groups on the proline fragment **338** and hydroxyl acid **337** is very crucial. A differential protection of these three hydroxy groups in the tetrapeptide of depsilairdin might be required in order to achieve the desired chemical transformations.

It is noteworthy that the syntheses of lairdinol A (**51**) and protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline (**338**) fragments have not been reported while fragments **337**[86] and **60**[82, 83] are known and are readily prepared from D-valine and L-valine respectively. Thus the first challenges were to design and establish efficient syntheses of **51** and **338** and direct them towards the preparation of depsilairdin (**55**).

**Scheme 2.1**. Retrosynthesis of depsilairdin (**55**).



### 2.2.2 Enantiospecific total synthesis of lairdinol A[†]

Lairdinol A belongs to the eudesmane family of sesquiterpenes.[116, 117] This class of natural products has attracted considerable attention from synthetic chemists.[118, 119] Several approaches have been documented in the literature concerning the synthesis of

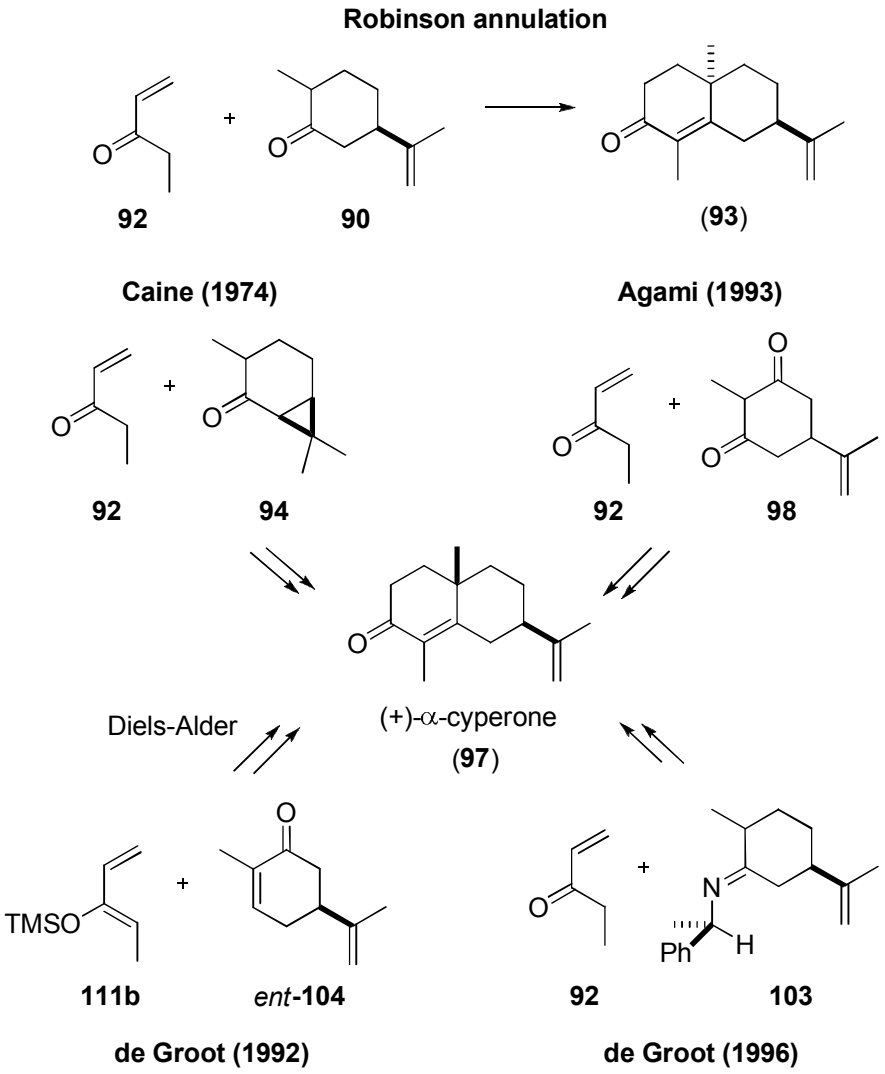


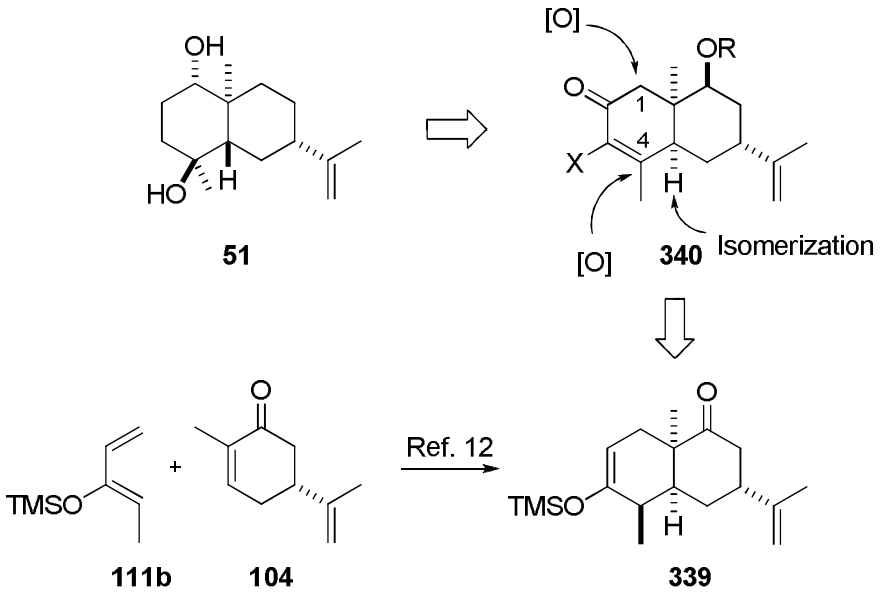

**Figure 2.2.** Approaches towards the synthesis of (+)-α-cyperone.

[†] This discussion of the enantiospecific total synthesis of lairdinol A is adapted from the published manuscript: *J. Org. Chem.* **2008**, *73*, 1071.

eudesmane type sesquiterpenes. The decalin ring system can be constructed via a Robinson annulation of dihydrocarvone (**90**) as starting material.[118-120] However, this method places the angular methyl and the isopropenyl groups trans to each other. Other approaches where these two groups are cis to each other as required in lairdinol **51** are also known and are briefly elaborated in Figure 2.2.[†] Although numerous eudesmanoids have been synthesized, the oxidation pattern and relative configuration of lairdinol A (**51**) are somewhat unusual and synthetic efforts relevant to this structure are scarce.[55]

The Diels-Alder reaction of (*R*)-carvone (**104**) with diene (**111b**),[121] previously reported by de Groot *et al.*,[54] afforded an attractive means to assemble the complete carbon skeleton of **51** in enantiopure form in a single operation. Surprisingly, this approach has not been applied to eudesmane syntheses presumably because of real or

**Scheme 2.2.** Retrosynthesis of lairdinol A (**51**).




[†] A detailed account of these approaches is discussed in section 1.3.1.2 on page 22.

perceived difficulties in introducing the desired functionality.[†] The approach to lairdinol A (**51**) is outlined in Scheme 2.2.

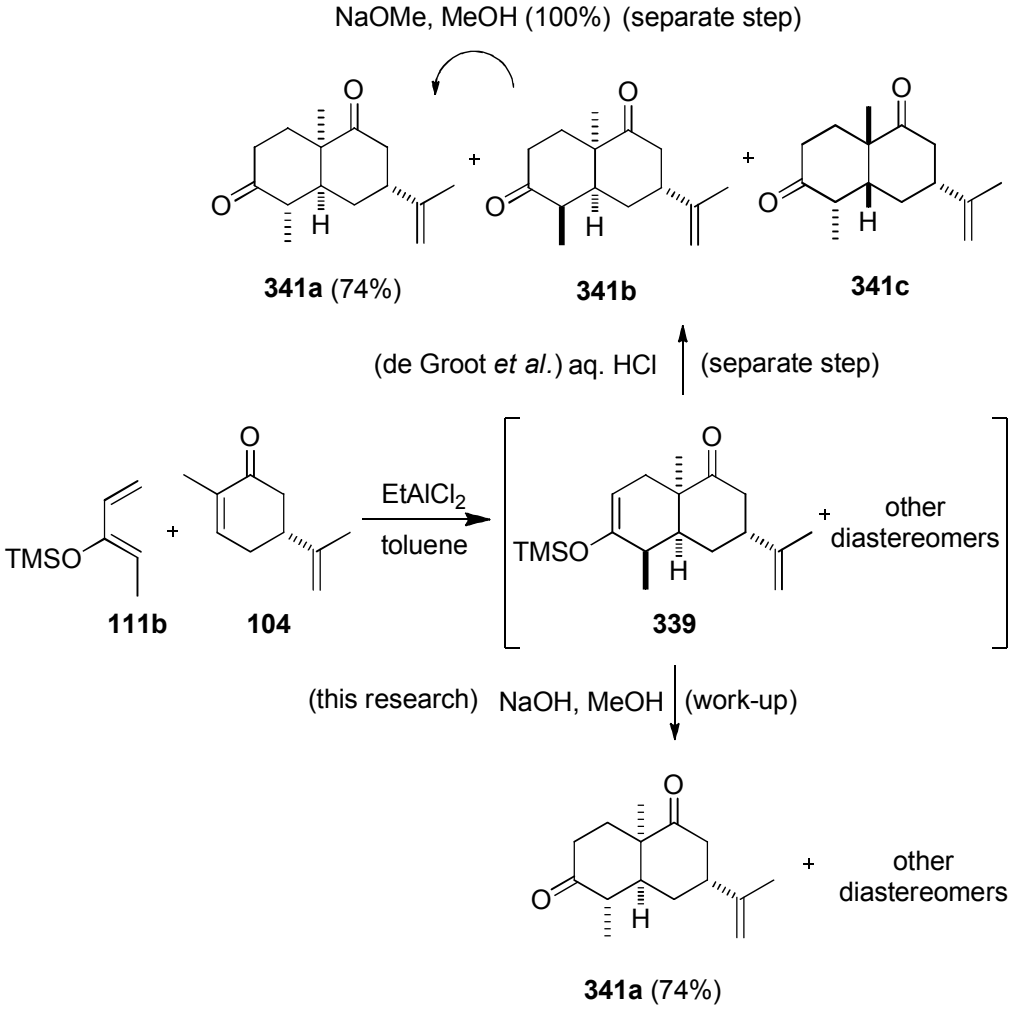
It was decided to take advantage of the enol ether in the initially formed Diels-Alder adduct **339** to effect a regioselective oxidation en route to an enone derivative represented in general terms by structure **340**. The enone functionality in **340** was expected to (i) allow isomerization of the cis ring fusion using the steric bulk of the -OR substituent to favor the desired trans isomer[122] and (ii) facilitate stereoselective introduction of the required hydroxyl groups at C-1 and C-4 (eudesmane numbering). Of course, reductive removal of the oxygen-based functional groups present in **340** would also be required for its conversion to lairdinol A (**51**).

The Diels-Alder reaction[54] of **111b** with **104** under the reported conditions using $EtAlCl_2$ gave a mixture of diastereomers **341a**, **341b** and **341c** in variable ratio.[¶] Unfortunately, attempts to directly isolate the enol ether **339** resulted in substantial hydrolysis.[123] The major product **341b** is quantitatively isomerized to **341a** by NaOMe according to de Groot. In a modification of the de Groot procedure,[54] the Diels-Alder reaction was quenched by addition of methanolic NaOH, which served to hydrolyze the TMS enol ethers in the adducts and to isomerize the product derived from the major adduct **339** to give **341a** in 74% yield (87% conversion) after chromatography (Scheme 2.3).

[†] However, this method was used to prepare (+)-α-cyperone (**97**) in 40% yield over 7 steps from (*S*)-carvone. Although various eudesmanes have been prepared from α-cyperone, this route is longer and less efficient than others (See Figure 2.2).

[¶] Epimerization of **341b** to **341a** took place upon hydrolysis.

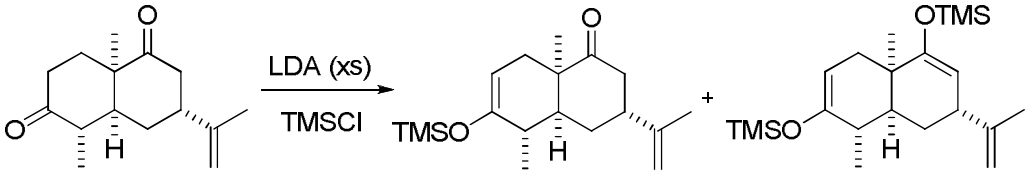
**Scheme 2.3.** Access to the complete carbon skeleton of lairdinol A by Diels-Alder reaction.




The next objective was to isomerize the ring junction in **341a** from cis to trans. This might be achieved via an enone like **340** (Scheme 2.2). Conversion of **341a** to **340** was planned to proceed by selective α-hydroxylation of **341a** followed by oxidation to give diosphenol **348** (X = OH). Several experiments were conducted to assess the possibility of chemoselective enolization of compound **341a** using LDA. Reactions were conducted by using various amounts of LDA and it was found that the regioselectivity of

enolization was insufficient to obtain a high yield of **342** (Table 2.1). However, bis(TMS enol ether) **343** was obtained in quantitative yield when excess LDA was employed.

**Table 2.1**. Attempted regioselective enolization of **341a**.

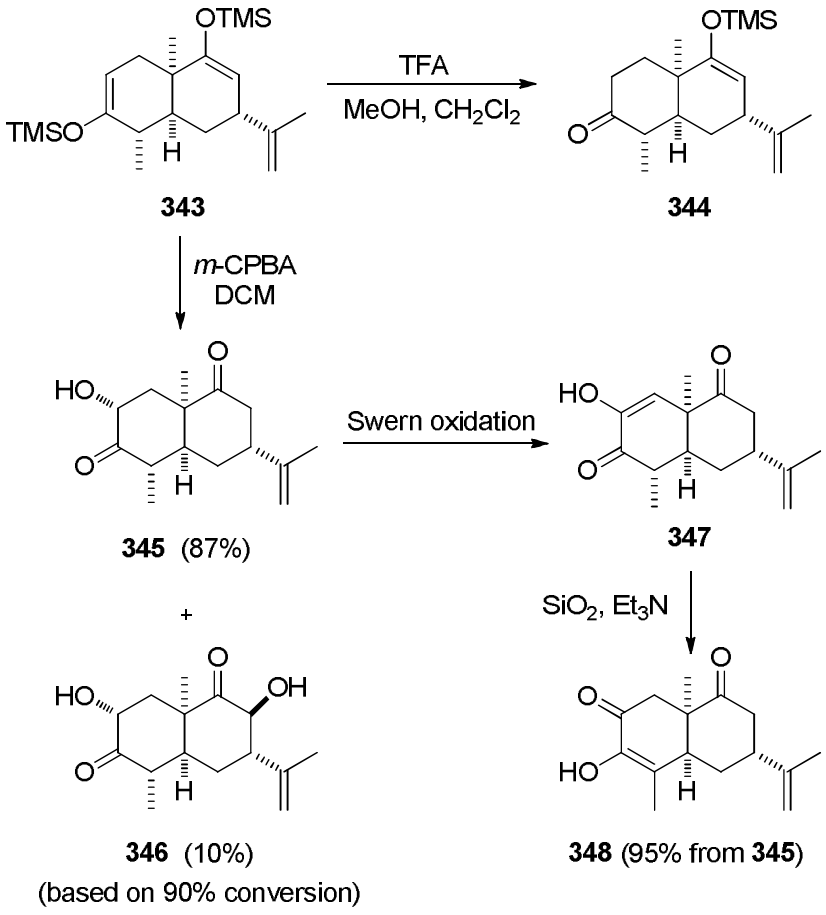



**341a** **342** **343**

| Equiv. of LDA | Ratio of 341a : 342 : 343 |
|---|---|
| 1.5 | 47 : 47 : 06 |
| 2.0 | 14 : 49 : 37 |
| 3.0 | 00 : 00 : 100 |

Mild hydrolysis of **343** was attempted as an alternative means for obtaining **342**. However, the undesired regioisomer **344** was obtained with good selectivity. This result suggested that the desired enol ether was the more reactive. Gratifyingly, regioselective oxidation of **341a** was achieved by treatment of the bis(TMS enol ether) **343** with *m*-CPBA (1.2 equiv) to give recovered **341a** (10%), diol **346**, and **345** (78%; 87% based on 90% conversion).[124] Swern oxidation of **345** gave the corresponding trione that was primarily in the undesired enol form **347** (**347**:**348** ca. 10:1 by $^{1}$H NMR); however, simply passing this material through a column of basic silica gel resulted in complete isomerization to **348** (95% from **345**) (Scheme 2.4).

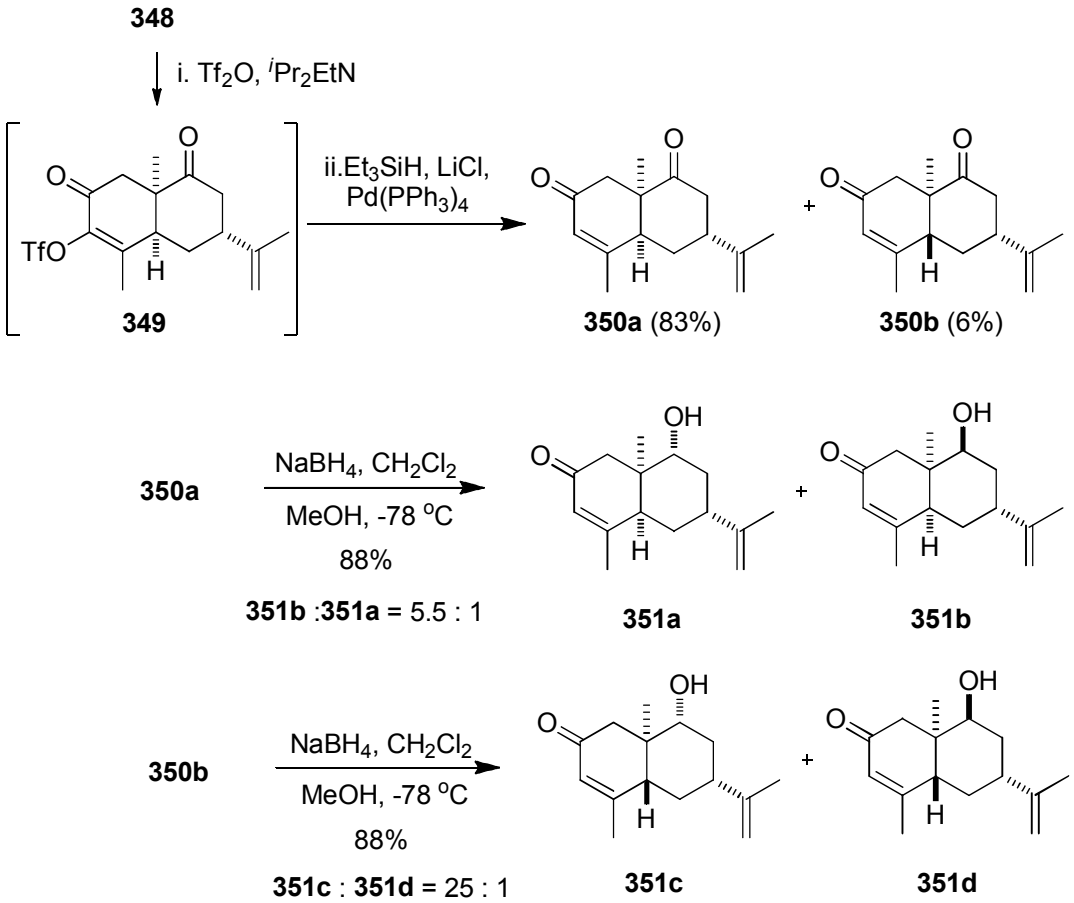
**Scheme 2.4**. Regioselective oxidation of bis(TMS enol ether) (**343**).




All attempts to isomerize the ring junction in **348** by treatment with base failed. Deoxygenation of the enol in **348** was considered as the next option. The desired deoxygenation was smoothly achieved by Pd-catalyzed reduction of the corresponding triflate (**349**) to give a separable 13:1 mixture of **350a** and **350b**, respectively (Scheme 2.5).[125] Unfortunately, attempted isomerization of **350a** to **350b** under basic conditions led only to decomposition, likely due to autoxidation (*vide infra*). Alternatively, chemoselective reduction[126] of the saturated ketone in **350a** using $NaBH_4$ in $CH_2Cl_2$/MeOH at low temperature to give a 5.5:1 mixture of **351b** and **351a**,

respectively, in excellent yield. Similar reduction of **350b** gave **351c** with high diastereoselectivity.

**Scheme 2.5**. Synthesis of hydroxyenones **351**.

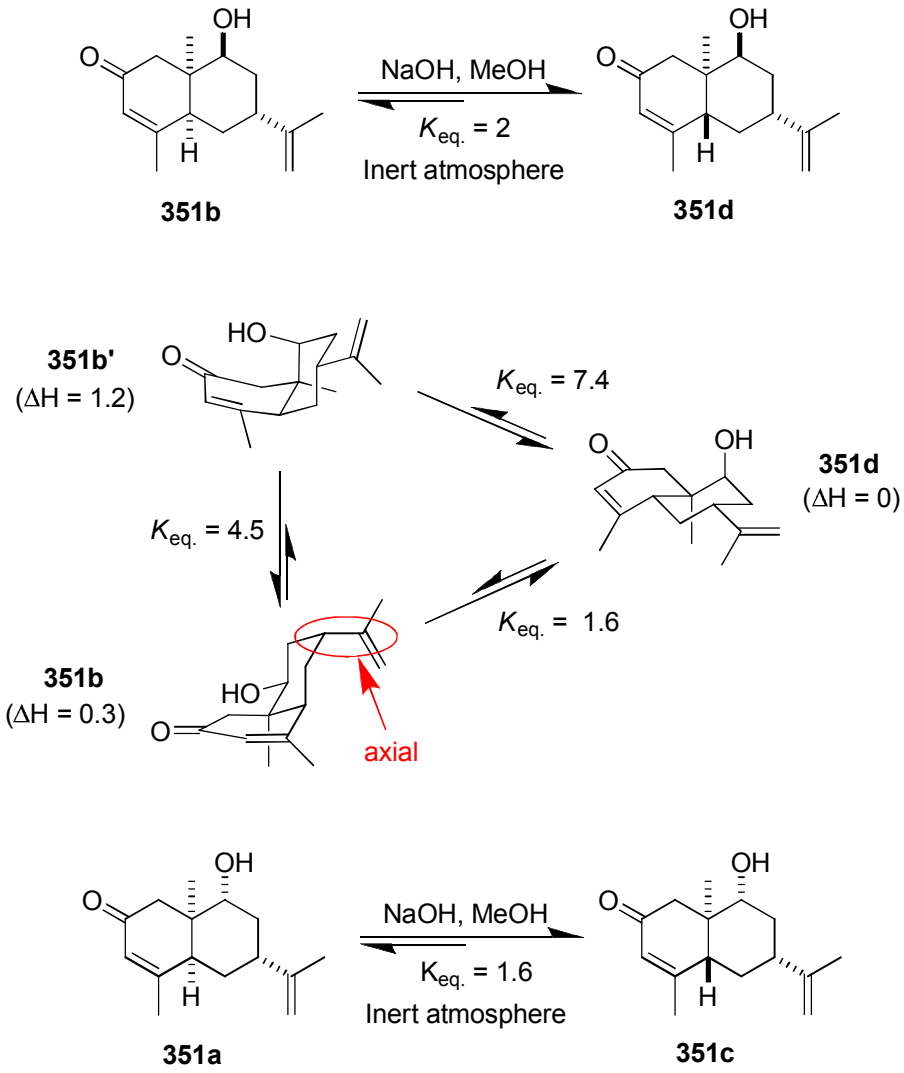



Isomerization of **351b** or **351d** in degassed methanolic NaOH under inert atmosphere led to a 2.0:1 equilibrium mixture of the two diastereomers favoring the desired **351d**. This equilibrium constant was much smaller than was initially anticipated based on molecular mechanics calculations[†] performed by Dr. D. E. Ward assuming only conformers of **351b** and **351d** with the isopropenyl group in an equatorial orientation

[†] Molecular mechanics calculations were performed by Dr. D. E. Ward using CaChe, version 3.9.

(Scheme 2.6). However, the $^{1}$H NMR spectrum of **351b** clearly indicated that the major conformer had the -OH group in an equatorial orientation (HC-8: br d, $J$= 9 Hz) and the isopropenyl group in an axial orientation (HC-6: br s, $w_{1/2}$= 15 Hz). Molecular mechanics calculations[†] performed by Dr. D. E. Ward predicted the conformer of **351b** with an axial

**Scheme 2.6**. Isomerization studies on **351b** and **351a**.



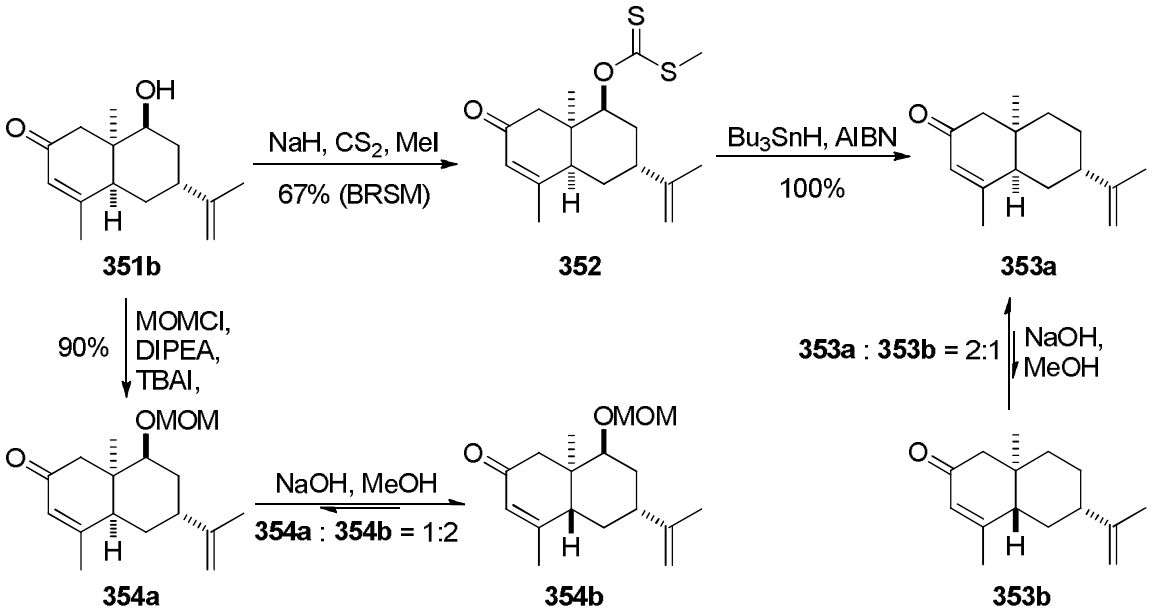

isopropenyl group was only ca. 0.3 kcal/mol less stable than **351d**. Thus, considering conformers of **351b** with both axial and equatorial isopropenyl groups, the predicted *K*eq

[†] Molecular mechanics calculations were performed by Dr. D. E. Ward using CaChe, version 3.9.

is ca. 1.3 in favor of **351d** and the observed equilibrium constant can be rationalized by considering this conformer. Similar isomerization of **351c** gave a 1.6:1 mixture of **351c** and **351a**, respectively.

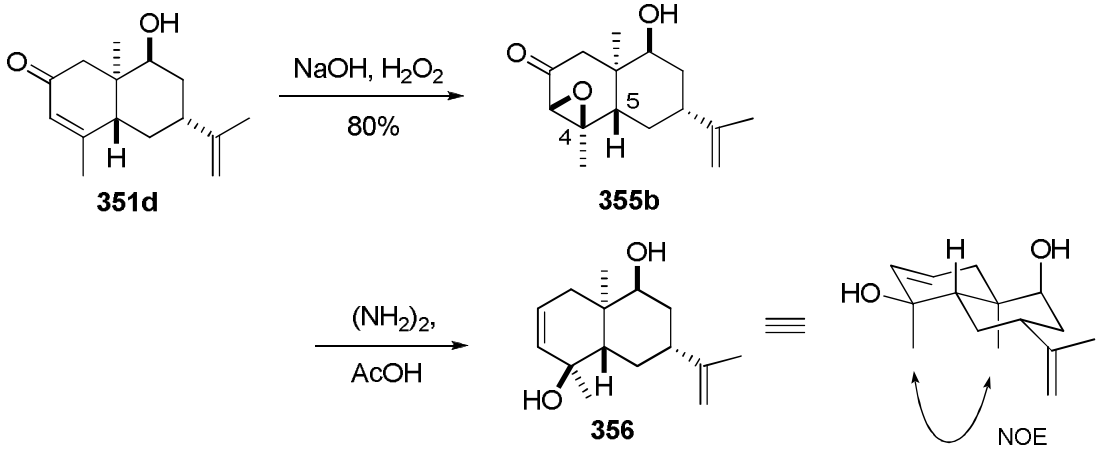
The modest equilibrium constants in favor of the desired trans-fused diastereomers (**351b** and **351c**) represented a serious obstacle to the feasibility of the planned synthetic route. The relatively unfavorable equilibrium ratio of **351b** : **351d** and the difficulty in their separation necessitated further investigation. Altering the -OH group was considered as a potential strategy to improve the isomerization. Thus xanthate **352** was prepared and subjected to Barton-McCombie deoxygenation[127] using $Bu_3SnH$ in the presence of AIBN to give **353a** (Scheme 2.7). Unfortunately, subjecting **353a** or **353b** to NaOH/MeOH gave a 2:1 equilibrium ratio favoring **353a**. Similarly, the MOM protected alcohol **354a** was prepared from **351b** and subjected to methanolic NaOH but gave a disappointing 1 : 2 mixture of **354a** : **354b**.

**Scheme 2.7**. Synthesis and isomerizations of **353a** and **354a**.



Returning to the isomerization of **351b**, separation of the 2:1 mixture of diastereomers **351d** and **351b**, respectively, was achieved by PTLC using 30% hexane in diethyl ether. Epoxidation of **351d** using hydrogen peroxide in the presence of NaOH gave **355b** in good yield (Scheme 2.8). The relative configuration of the epoxide in **355b** was determined by $^1$H NMR analysis of the allylic alcohol **356** obtained by treatment of **355b** with hydrazine (Wharton reaction).[128] NOE experiments on **356** indicated that the methyl groups were cis to each other. It was noteworthy that the absolute configurations of all stereocenters in **356** were identical to those in lairdinol A.

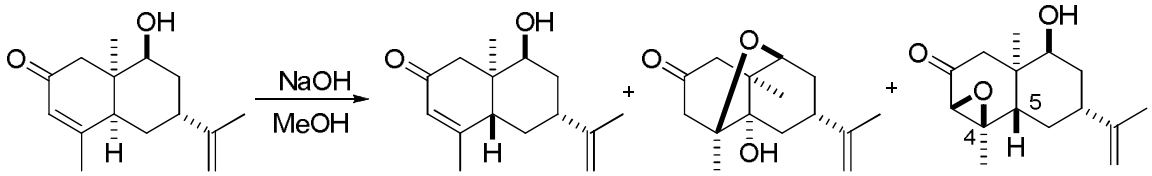
**Scheme 2.8**. Epoxidation of **351d** and determination of relative configuration at C-4.




In an effort to optimize the isomerization of **351b**, the rate of reaction was assessed by removing aliquots and analyzing them by $^1$H NMR. A 2:1 equilibrium mixture of **351d** and **351b** was observed after 16 h; however two side products were also formed (Table 2.2). The side products were isolated and identified as **355b** and **357**. Suspecting that these oxidation products resulted from exposure of the reaction mixture to air when removing aliquots, the isomerization of **351b** was conducted under air.

Under these conditions, **355b** and **357** were produced in >70 % yield after 3 days. The stereoselective formation of the trans epoxide **355b** was of particular interest as this product incorporates the stereogenic centers at C-4 and C-5 in **51** (eudesmane numbering) with the correct relative configurations.

**Table 2.2.** Base catalyzed isomerization and autoxidation of **351b**.




**351b** **351d** **357** **355b**

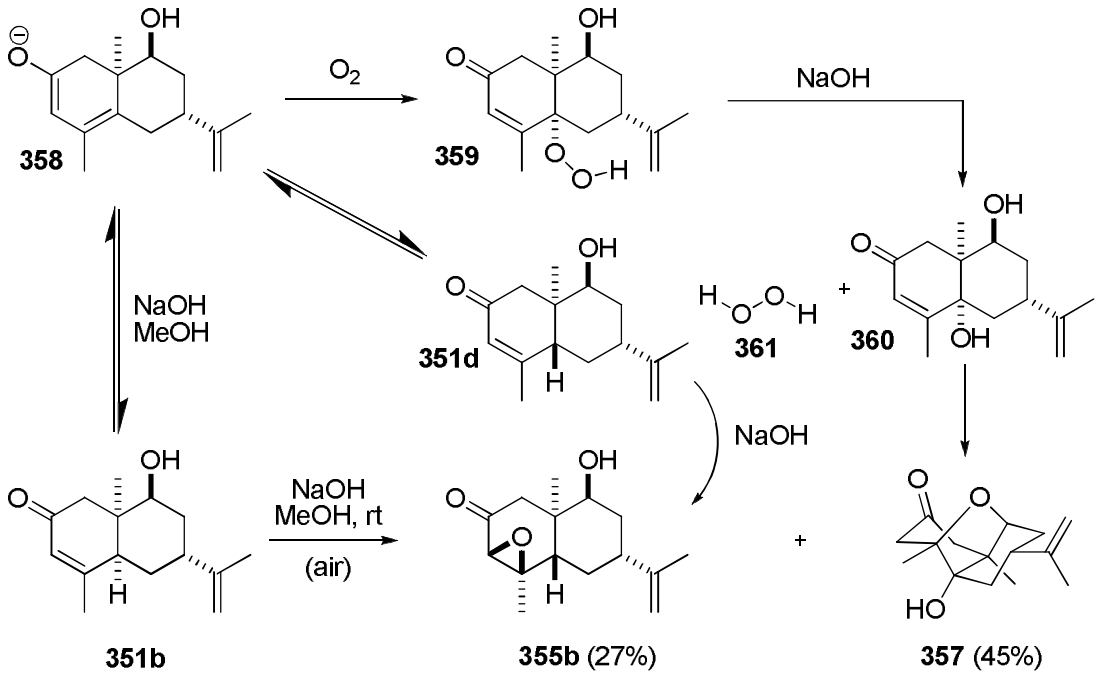
| Time[a] (h) | Ratio of compounds observed (by $^1$H NMR) | | | |
|---|---|---|---|---|
| | **351b** | **351d** | **357** | **355b** |
| **8** | 40 | 52 | 2 | 6 |
| **16** | 30 | 56 | 4 | 10 |
| **32** | 27 | 46 | 11 | 16 |
| **68** | 26 | 36 | 20 | 18 |

[a] Aliquots were removed at the indicated times exposing the reaction to air

Base-catalyzed autoxidation of enones is well-known.[129, 130] Under the basic reaction conditions, **351b** and **351d** are equilibrated via their common dienolate **358** (Scheme 2.9). In analogy to the proposal of Frimer *et al.*,[130] this dienolate can react with molecular oxygen at the $\gamma$-position to provide a hydroperoxide intermediate that can epoxidize **351d** to give **355b** and **357** (after cyclization of the hydroxyenone) (Scheme 2.9). Regardless of the actual mechanism, this result suggested that epoxidation of **351d** was much more facile than that of **351b**. Thus, deliberate epoxidation of cis **351b** under

conditions where its oxidation was slower than isomerization to trans **351d** should selectively lead to the desired trans **355b**.

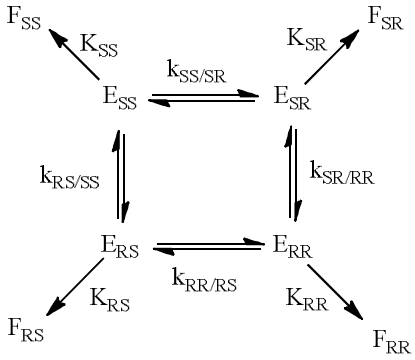
**Scheme 2.9**. Autoxidation of enone **351b**.




Following the above hypothesis, treatment of **351b** with $H_2O_2$ and excess NaOH in methanol solution gave **355b** in 78% yield after optimization of the reaction conditions (Scheme 2.10). The use of excess base was necessary to maintain a useful rate of isomerization of **351b**. The resulting facile epoxidation of **351d** under conditions where

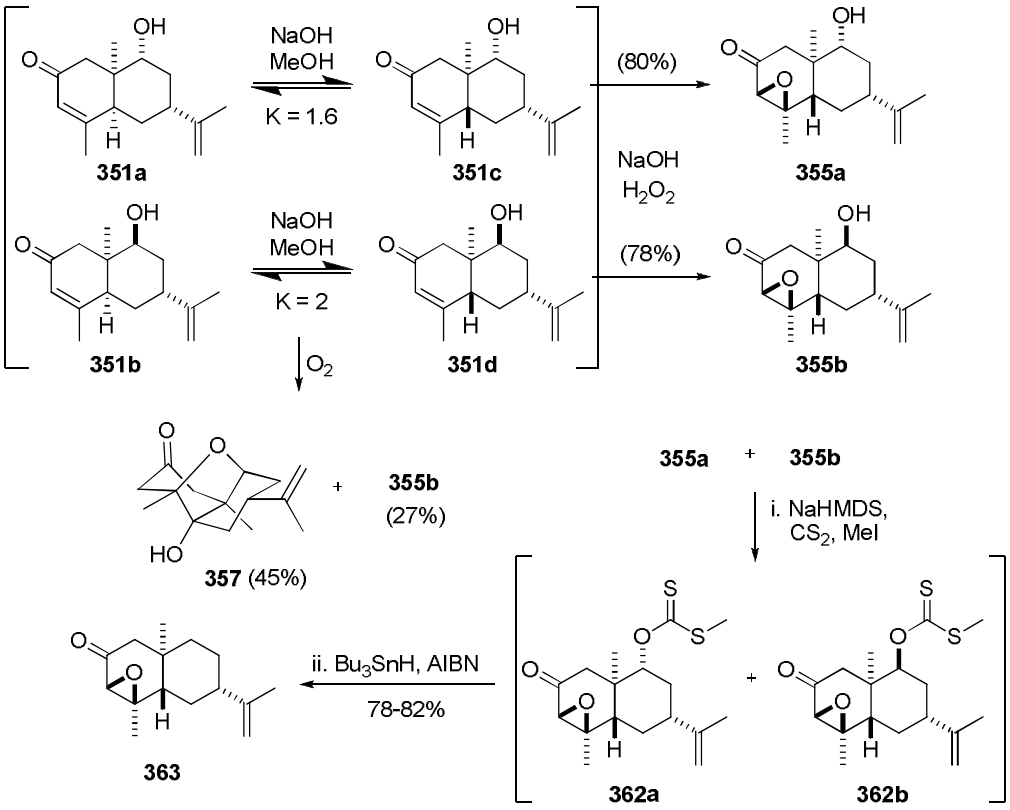
**351b** and **351d** are equilibrating constitutes a (type III) dynamic kinetic asymmetric transformation (DYKAT)† of these diastereomers.[131] Similar epoxidation of **351a** gave **355a** in 80% yield. Barton-McCombie deoxygenations[127] of **355a** and **355b** gave **363** in excellent yields. Because all of the diastereomers of **350**, **351**, and **355** were ultimately converted into **363** using the same protocols, diosphenol **348** was converted into **363** in 46% overall yield without separation of the stereoisomers formed in the intermediate stages (Scheme 2.11).

† Steinreiber *et al*. has defined DYKAT (Dynamic Kinetic Asymmetric Transformations) as follows: "The de-symmetrization of racemic or diastereomeric mixtures involving interconverting diastereomeric intermediates - implying different equilibration rates of the stereoisomers - is termed dynamic kinetic asymmetric transformation."[131] The transformation of **351** to **355** constitutes a (type III) dynamic kinetic asymmetric transformation (DYKAT) see figure below.[131]

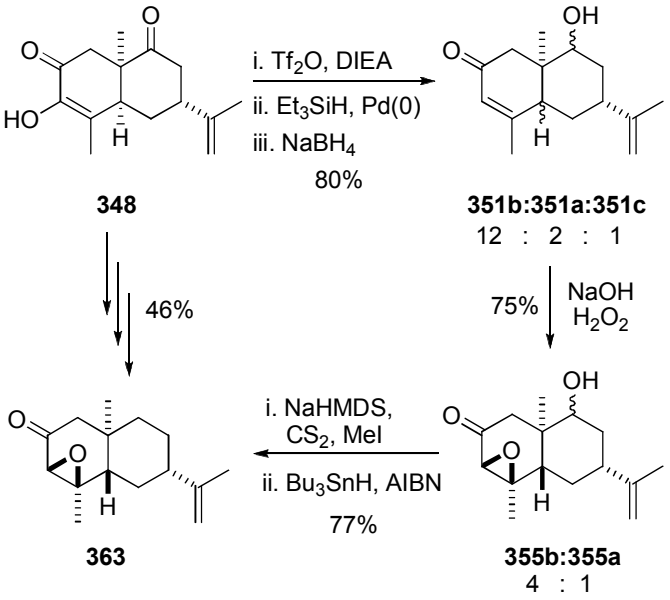



DYKAT type III with simplified epimerization rates. $E_{RS}/E_{SR}$ & $E_{RR}/E_{SS}$=enantiomeric pairs of diastereomeric initial products; $F_{RS}/F_{SR}$ & $F_{RR}/F_{SS}$=enantiomeric pairs of diastereomeric final products; $k_{SS}/k_{SR}$ through $k_{RS}/k_{SS}$=equilibration rates of formation $E_{SS}/E_{SR}/E_{RR}/E_{RS}$; $k_{RR}$ through $k_{SS}$= rates of irreversible formation of $F_{RS}/F_{SR}$ & $F_{RR}/F_{SS}$ (Figure taken from Ref. 131). However, for the current reactions (i.e., **351a** → **355a**; **351b** → **355b**) only the top half of the figure applies: $E_{SS}$ = **351a** or **351b**; $E_{SR}$ = **351c** or **351d** which gives the product $F_{SR}$ = **355a** or **355b**.

**Scheme 2.10**. Synthesis of epoxy-ketone **363** via DYKAT of **351**.



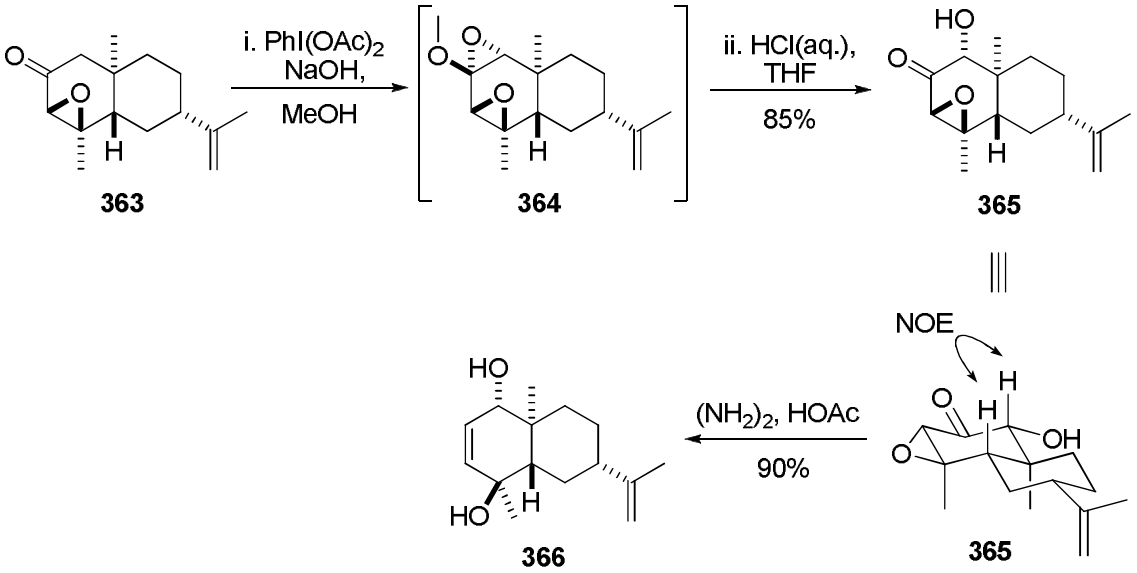

**Scheme 2.11.** Conversion of **348** to **363**.




Stereoselective hydroxylation of epoxyketone **363** was effected by treatment with

$PhI(OAc)_2$ in basic methanol followed by acid hydrolysis of the intermediate methoxyepoxide **364** to give ketol **365** as the only detectable isomer (Scheme 2.12).[124, 132, 133] It was noteworthy that the relative configuration of the -OH group in the epoxy-alcohol **365**, determined by NOE, was identical with that in lairdinol A (**51**). Wharton reaction[128] of **365** readily gave the allylic diol **366**.

**Scheme 2.12.** Synthesis of diol **366**.

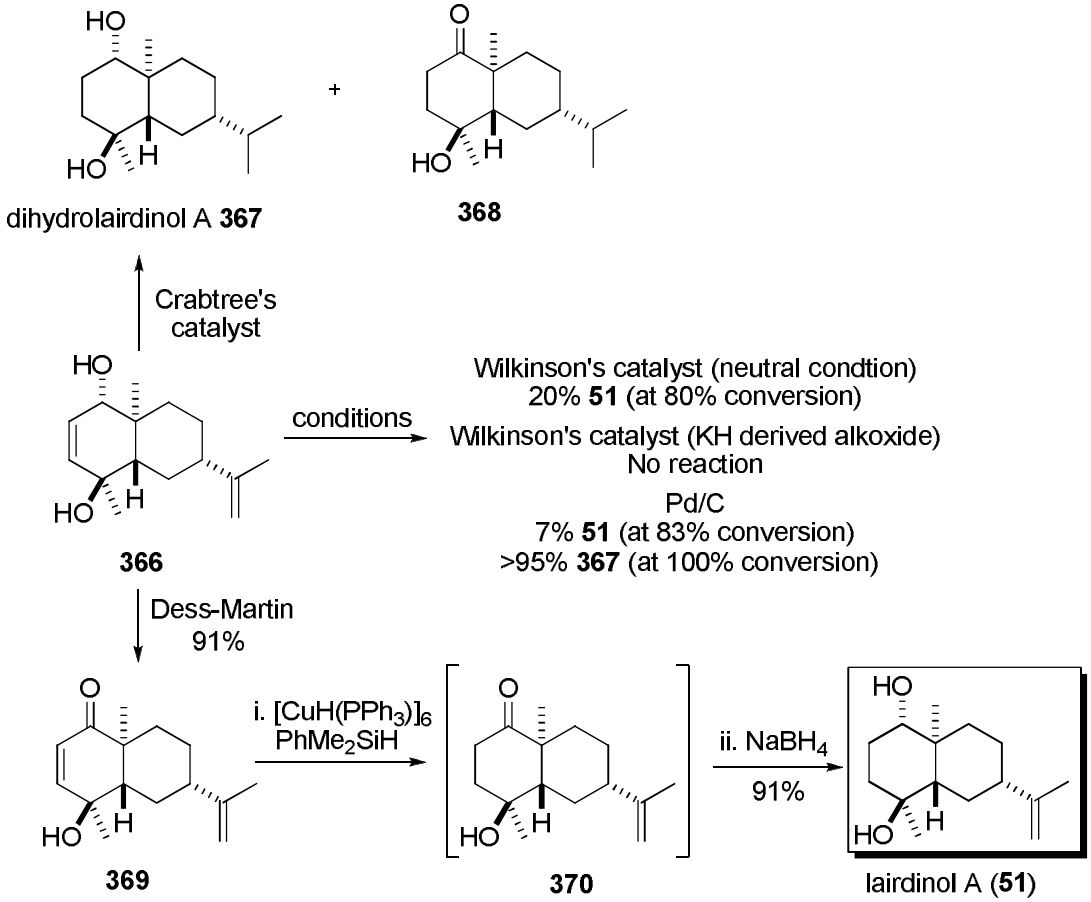



At this stage the direct conversion of **366** into **51** was attempted by exploiting hydroxyl-directed[134, 135] hydrogenation to achieve chemoselective saturation of the allylic alcohol in the presence of the isolated alkene (Scheme 2.13).[136-139] Unfortunately, all attempts using $[Ir(cod)(PCy)_3(py)]PF_6$,[140, 141] $RhCl(PPh_3)_3$,[142] or Pd-C[143] catalysts failed; in each case, reduction of the isopropenyl group was faster than that of the allylic alcohol. With the Crabtree catalyst,[†] ca. equal amounts of dihydrolairdinol A (**367**) and the

[†] Reactivity and protocol validated using 3,5,5-trimethylcyclohex-2-en-1-one.[31]

corresponding ketone **368**[¶] were obtained. Using Wilkinson's catalyst, no reaction was observed with the KH-derived alkoxide of **366**.[142] Under neutral conditions, **51** (obtained in <20% yield at 80% conversion) was the minor product even at low conversion; however, the obtention of **51** confirmed the stereochemical configuration assigned to **366**. Formation of **51** (<7% at 83% conversion) was even less favored with Pd-C as the

**Scheme 2.13**. Hydrogenation of compound **366** and completion of lairdinol A (**51**).




catalyst; however dihydrolairdinol A (**367**) could be obtained in high yield under these conditions (Scheme 2.13). The desired transformation of **366** was efficiently achieved by

[¶] **368** results from rearrangement rather than hydrogenation of the cyclohexene in **366**.

Dess-Martin oxidation to enone **369** followed by catalytic Cu(I)-mediated conjugate reduction[144-146] with a $NaBH_4$ workup to give **51** in 83% overall yield from **366**. Spectroscopic and chiroptical properties of synthetic **51** were essentially identical with those reported for the natural product. As indicated in section 1.3.1.1 (page 23), the spectral data of cyperusol C (*ent*-**51**) as reported by Xu[42] was taken in $CDCl_3$ while that of lairdinol A (**51**)[19] was obtained in $C_6D_6$. The $^1H$ NMR and $^{13}C$ NMR of both natural products in respective solvents are given below for comparison. The $^1H$ chemical shifts for synthetic **51** are essentially identical to those reported by Xu *et al.*[42] however, the $^{13}C$ chemical shifts for synthetic **51** are consistently higher by 0.3 ppm presumably due to a different assignment of the reference frequency (Value of $\delta_C$ = 77.23 for $\underline{C}DCl_3$ were used in the current study).


lairdinol A (**51**) cyperusol C (*ent*-**51**)

**Figure 2.3**. Structures of lairdinol A and cyperusol C.

**Table 2.3.** NMR data of synthetic lairdinol A and natural cyperusol C in $CDCl_3$.

| **$^1$H NMR ($CDCl_3$)** | | **$^{13}$C NMR ($CDCl_3$)** | |
|---|---|---|---|
| **Synthetic lairdinol A** | **Cyperusol C** | **Synthetic lairdinol A** | **Cyperusol C** |
| 4.73-4.71 (2H, m, $H_2C$=C) | 4.72 (2H, m, $H_2C$=C) | 150.5 (s, C=$CH_2$) | 150.3 (s, C=$CH_2$) |
| 3.34 (1H, dd, *J* = 4, 11 Hz, HC-4) | 3.32 (1H, dd, *J* = 4.4, 11.2 Hz, HC-4) | 108.6 (t, $CH_2$=C) | 108.3 (t, $CH_2$=C) |
| 1.94 (1H, dddd, *J* = 3.5, 3.5, 11.5, 11.5 Hz, HC-7) | 1.94 (1H, m, HC-7) | 79.6 (d, C-4) | 79.3 (d, C-4) |
| 1.90 (1H, ddd, *J* = 3.5, 3.5, 12.5 Hz, HC-5) | 1.90 (1H, ddd, *J* = 3.5, 3.5, 13.5, HC-5) | 71.8 (s, C-1) | 71.6 (s, C-1) |
| 1.87-1.83 (1H, m, HC-8) | 1.84 (1H, m, HC-8) | 53.2 (d, C-8a) | 52.9 (d, C-8a) |
| 1.81 (1H, ddd, *J* = 3.5, 3.5, 12.5 Hz, HC-2) | 1.79 (1H, ddd, *J* = 3.0, 3.5, 12.0 Hz, HC-2) | 45.9 (d, C-7) | 45.7 (d, C-7) |
| 1.76 (3H, s, $H_3CC$=C) | 1.75 (3H, s, $H_3CC$=C) | 41.1 (t, C-2) | 40.8 (d, C-2) |
| 1.74 (1H, m, HC-3) | 1.72 (1H, m, HC-3) | 40.8 (t, C-5) | 40.5 (t, C-5) |
| 1.66-1.56 (2H, m, HC-3, HC-6) | 1.62 (1H, m, HC-3) | 39.2 (s, C-4a) | 38.9 (s, C-4a) |
| | 1.61 (1H, m, HC-6) | 28.8 (t, C-3) | 28.5 (t, C-3) |
| 1.52 (1H, ddd, *J* = 3.5, 13.5, 13.5 Hz, HC-2) | 1.52 (1H, ddd, *J* = 3.5, 12.0, 13.5 Hz, HC-2) | 26.6 (t, C-6) | 26.4 (t, C-6) |
| 1.38 (1H, dddd, *J* = 3.5, 13, 13.5, 17 Hz,HC-6) | 1.38 (1H, dddd, *J* = 3.5, 13.0, 13.5, 17.0 Hz, HC-6) | 26.0 (t, C-8) | 25.7 (t, C-8) |
| 1.32-1.24 (2H, m, HC-8, HC-8a) | 1.28 (1H, m, HC-8a) | 23.0 (q, $CH_3C$-1) | 22.7 (q, $CH_3C$-1) |
| | 1.26 (1H, m, HC-8) | 21.2 (q, $CH_3C$=C) | 21.0 (q, $CH_3C$=C) |

| | | | |
|---|---|---|---|
| 1.16 (1H, ddd, *J* = 4, 13, 13 Hz, HC-5) | 1.13 (1H, ddd, *J* = 4.0, 13.0, 13.5 Hz, HC-5) | 13.3 (q, $CH_3C$-4a) | 13.0 (q, $CH_3C$-4a) |
| 1.14 (3H, s, $H_3CC$-1) | 1.11 (3H, s, $H_3CC$-1) | | |
| 0.90 (3H, s, $H_3CC$-4a) | 0.89 (3H, s, $H_3CC$-4a) | | |

**Table 2.4.** Spectral data of synthetic and natural lairdinol A in $C_6D_6$.

| **$^1$H NMR of lairdinol A ($C_6D_6$)** | | **$^{13}$C NMR lairdinol A ($C_6D_6$)** | |
|---|---|---|---|
| **Synthetic** | **Natural** | **Synthetic** | **Natural** |
| 4.86 (1H, br s, HC=C) | 4.96 (2H, d, *J* = 15 Hz, $H_2C$=C) | 150.8 (s, C=$CH_2$) | 150.6 (s, C=$CH_2$) |
| 4.83 (1H, br s, HC=C) | | 109.1 (t, $CH_2$=C) | 108.8 (t, $CH_2$=C) |
| 2.99 (1H, dd, *J* = 4.5, 11 Hz, HC-4) | 3.11 (1H, dd, *J* = 4, 11 Hz) | 79.7 (d, C-4) | 79.5 (d, C-4) |
| 1.93 (1H, dddd, *J* = 2, 2, 4, 13 Hz, HC-8) | 2.03 (1H, m, HC-8) | 71.3 (s, C-1) | 71.1 (s, C-1) |
| 1.89-1.82 (1H, m, HC-7) | 1.95 (1H, m, HC-7) | 53.6 (d, C-8a) | 53.3 (d, C-8a) |
| 1.83 (1H, ddd, *J* = 3, 3.5, 12.5 Hz, HC-5) | 1.85 (1H, ddd, *J* = 3, 3, 13 Hz, HC-5) | 46.6 (d, C-7) | 46.4 (d, C-7) |
| 1.71 (3H, s, $H_3CC$=C) | 1.82 (3H, s, $H_3CC$=C) | 41.8 (t, C-2) | 41.5 (t, C-2) |
| 1.58-1.52 (2H, m, HC-2, HC-6) | 1.67 (1H, m, HC-2) | 41.2 (t, C-5) | 41.0 (t, C-5) |
| | 1.65 (1H, m, HC-6) | 39.5 (s, C-4a) | 39.3 (s, C-4a) |
| 1.46-1.30 (3H, m, $H_2C$-3, HC-6) | 1.50 (1H, m, HC-3) | 29.5 (t, C-3) | 29.2 (t, C-3) |
| | 1.47 (1H, m, HC-6) | 27.3 (t, C-6) | 27.0 (t, C-6) |
| | 1.44 (1H, m, HC-3) | 26.5 (t, C-8) | 26.3 (t, C-8) |
| 1.26 (1H, ddd, *J* = 4.5, | 1.38 (1H, m, HC-2) | 23.1 (q, $CH_3C$- | 22.9 (q, $CH_3C$- |

| | | | |
|---|---|---|---|
| 13, 13 Hz, HC-2) | | 1) | 1) |
| 1.19 (1H, ddd, *J* = 12, 12.5, 12.5 Hz, HC-8) | 1.30 (1H, ddd, *J* = 12, 12, 12 Hz, HC-8) | 21.5 (q, $CH_3C$=C) | 21.2 (q, $CH_3C$=C) |
| 1.03 (1H, dd, *J* = 2.5, 12.5 Hz, HC-8a) | 1.15 (1H, dd, *J* = 2, 12 Hz, HC-8a) | 13.5 (q, $CH_3C$-4a) | 13.3 (q, $CH_3C$-4a) |
| 0.93 (1H, ddd, *J* = 3, 13, 13 Hz, HC-5) | 1.05 (1H, ddd, *J* = 3, 13, 13 Hz, HC-5) | | |
| 0.90 (3H, s, $H_3CC$-1) | 1.02 (3H, s, $H_3CC$-1) | | |
| 0.76 (3H, s, $H_3CC$-4a) | 0.88 (3H, s, $H_3CC$-4a) | | |

NMR spectra in $C_6D_6$ for synthetic **51** were essentially superimposable with those for natural **51** kindly provided by Prof. Pedras. However, compared to the reported values for natural **51**, the chemical shifts observed for synthetic **51** were consistently different ($\delta_H$, –0.11; $\delta_C$, +0.2) due to a different assignment of the reference frequency. Value of $\delta_H$ = 7.16 for $C_6\underline{H}D_5$ and $\delta_C$ = 128.39 for $\underline{C}_6D_6$ were used in the current study. Also, two typographical errors were identified in the previously reported $\delta_{Hs}$: 1.85 should be 1.95 (or 1.83 using $\delta_H$ = 7.16 for $C_6\underline{H}D_5$); 1.65 should be 1.55 (or 1.43 using $\delta_H$ = 7.16 for $C_6\underline{H}D_5$).

The absolute configuration for lairdinol A (**51**) was assigned based on its relationship with depsilairdin (**55**) and on the fact that they were isolated from the same fungal cultures.[19] The absolute configuration for **55** was assigned indirectly via a 2,5-morpholinedione degradation product.[25] The enantiomer of **51**, cyperusol C (*ent*-**51**), has been isolated from the plants *Cyperous longus*[42] and *Erigeron annus*.[43] The absolute configuration for *ent*-**51** was determined[42] using the advanced Mosher's method;[147]

however, the Δδ values reported are small[†] and it is known[147] that sterically hindered alcohols can give anomalous results. Unfortunately, the specific rotations reported for naturally occurring **51** and *ent*-**51** were obtained in different solvents. Taken together, the above facts raised some uncertainty about the proposed absolute configurations of the natural products.

The absolute configuration of synthetic **51** is firmly established by its synthetic relationship from (*R*)-carvone (**104**). Specific rotations for synthetic **51** were obtained under each of the reported conditions and these results fully confirm the assigned absolute configurations for **51** and *ent*-**51** (Table 2.5).

**Table 2.5**. Optical rotations of synthetic lairdinol A and natural samples.

| **Solvent** | $[\alpha]_D$ (*c* g/100mL) | | |
|---|---|---|---|
| | **Synthetic lairdinol A** | **Natural lairdinol A** | **cyperusol C** |
| $CH_2Cl_2$ | +18 (*c* 0.4) | +18 (*c* 0.4)[a] | - |
| MeOH | +34 (*c* 1.1) | - | -42.3 (*c* 1.10)[b] |
| $CHCl_3$ | +28 (*c* 1.3) | - | -25 (*c* 0.13)[c] |

[a]Ref 39. [b]Ref 38. [c]Ref 40.

In conclusion, the synthesis of lairdinol A (**51**) was achieved in 18% overall yield from (*R*)-carvone (**104**) over 12 linear steps. Novel features of the synthesis include; (i) the construction of the complete carbon skeleton via a Diels-Alder reaction, (ii) establishment of the trans ring junction by preferential epoxidation of a trans enone in an

[†] The Δδ values computed from the NMR data reported in ref 37 are different from those summarized in Figure 3 of that paper. In particular, the computed Δδ values for the four protons at C-2 and C-3 of *ent*-**51** (eudesmane numbering) are <0.01 ppm.

equilibrating mixture of the cis and trans diastereomers (DYKAT). It is also noteworthy that the entire synthesis proceeds without the use of protecting groups, a feature that has attracted interest recently.[148]

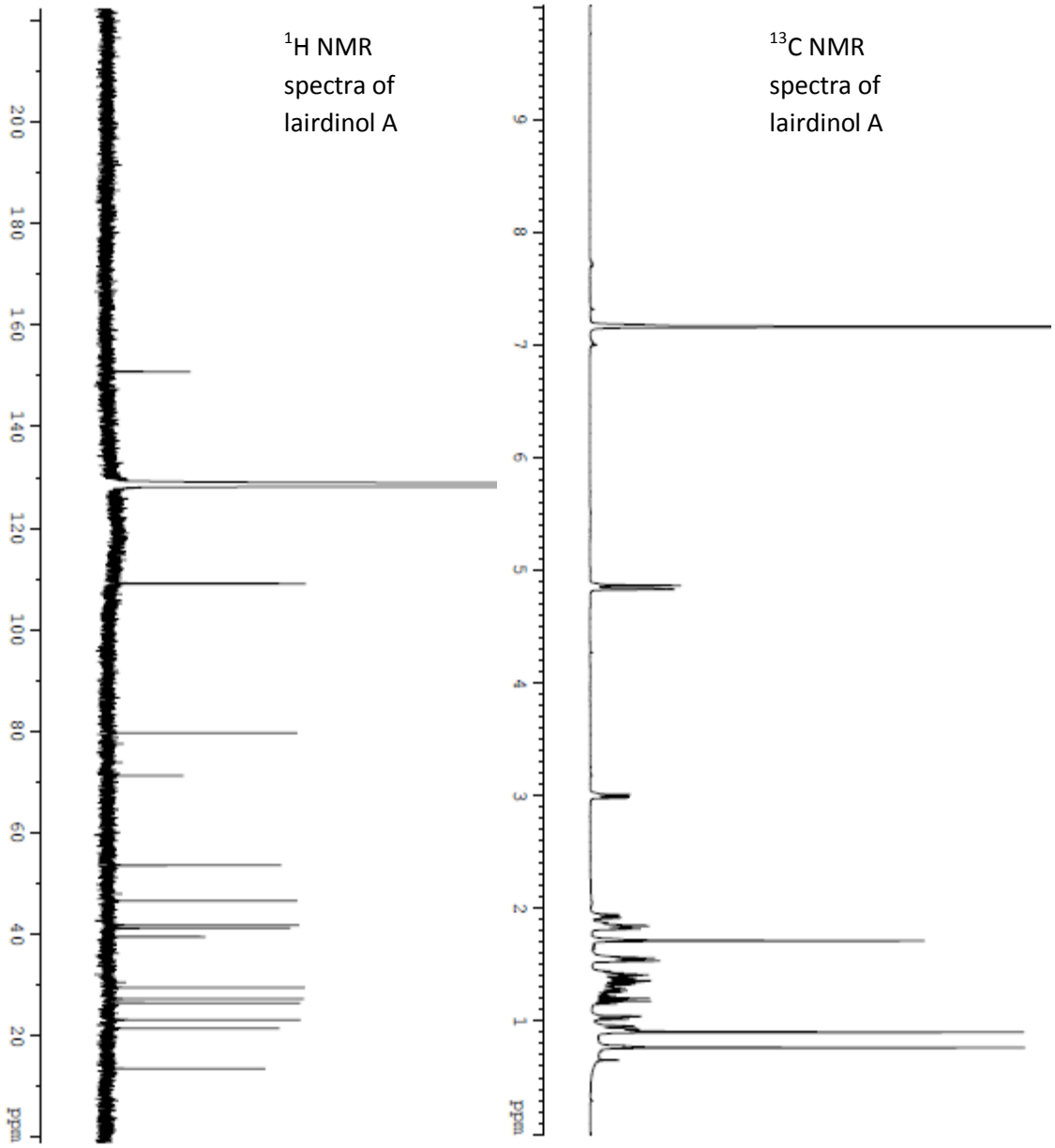



**Figure 2.4.** $^{1}$H and $^{13}$C spectras for synthetic lairdinol A.

### 2.2.3 Synthesis of protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline

Several desmethyl and deoxy analogues of (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline (**58**) have been prepared before and are well described in the literature (summaries in Figures 2.4 and 2.5).[†] Interestingly, Sardina and co-workers have disclosed the synthesis of triol **165** (from *trans*-4-hydroxy-L-proline) which is closely related to the desired proline fragment **58**. Easy access to **58** seemed feasible by adaptation of Sardina's route.

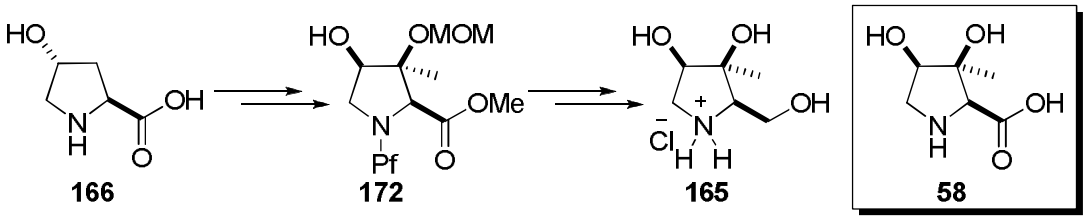



**Figure 2.5**. Sardina's approach towards triol **165**.

[†] For a detailed discussion see section 1.3.2, page 34.

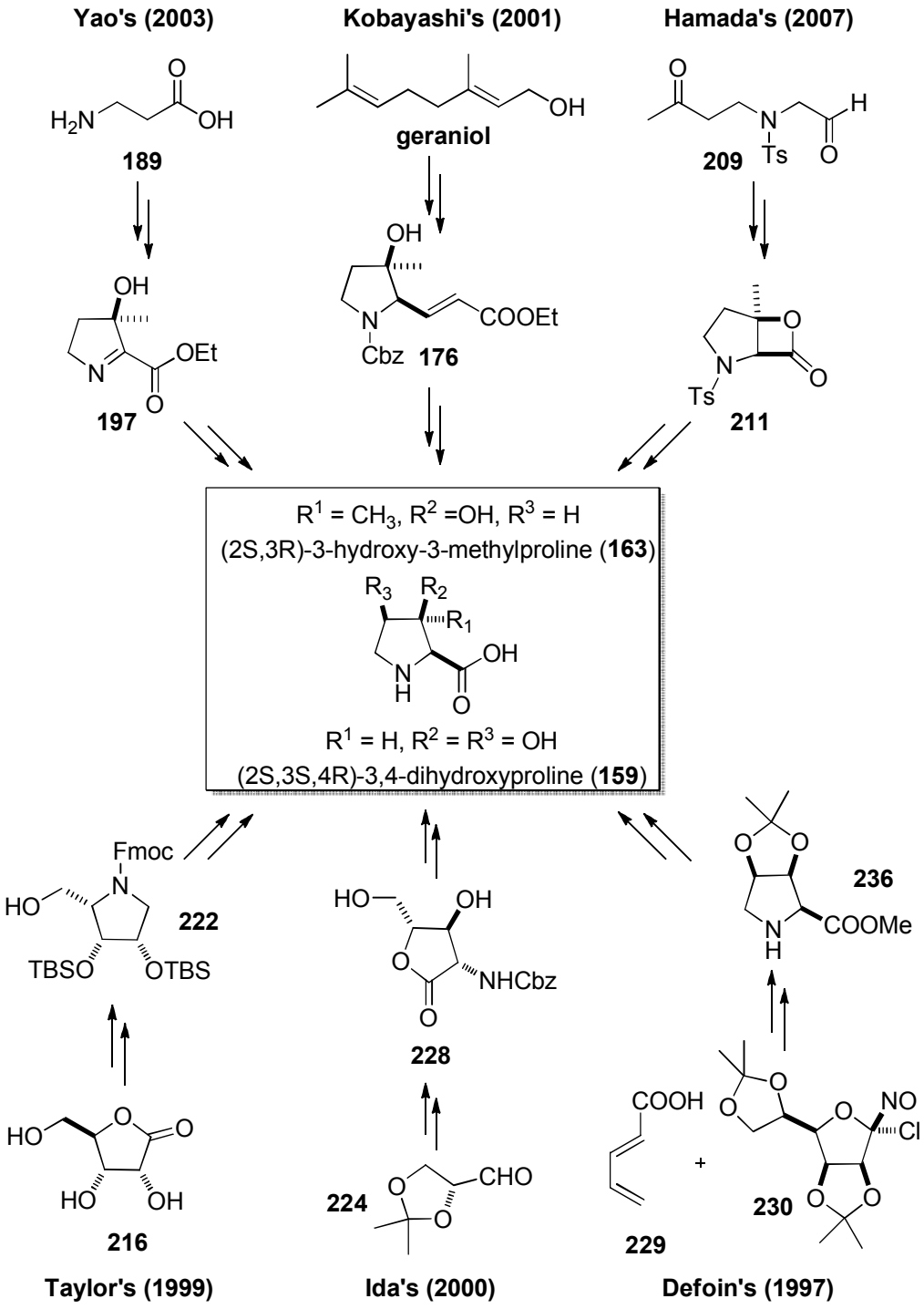
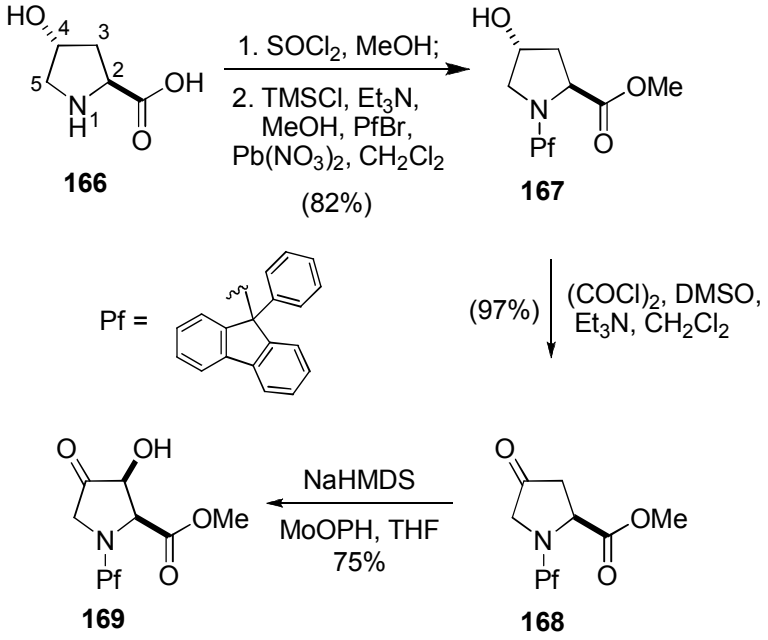



**Figure 2.6**. Approaches towards the synthesis of **159** and **163**.

*trans*-4-Hydroxy-L-proline (**166**) was converted to the corresponding methyl ester followed by *N*-protection to get ester-alcohol **167**. Swern oxidation of **167** followed by α-hydroxylation using Vedej's protocol[149] afforded keto-alcohol **169** in 60% overall yield from **166** (Scheme 2.14).[61, 62] As indicated in chapter one, the use of the very bulky –Pf (9-phenylfluorenyl) protecting group is essential to suppress deprotonation at the C-2 and C-5 positions in the proline fragment and to favour a ring conformation that places the ester group in the pseudo axial position, thereby directing the approach of the electrophile from the opposite face.[62]

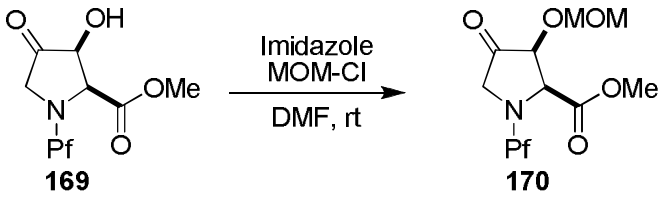
**Scheme 2.14**. Synthesis of alcohol **169**




The next step was to protect alcohol **169**. Sardina reported the desired transformation in an impressive 98% yield using 5 equiv. of MOM-Cl and 5 equiv. of imidazole in DMF at a concentration of 0.25 M.[62] However, when the reaction was

repeated according to Sardina's protocol, only the starting alcohol was recovered and the presence of desired product **170** was not detected (Table 2.6). Varying the stoichiometry of imidazole and MOM-Cl was next investigated. These experiments clearly showed that formation of the desired product **170** only occurred when an excess of MOM-Cl relative to imidazole was used and significant conversion required a ratio greater than 2:1. With excess MOM-Cl (5-6 equiv.) apparent high conversions to **170** were observed with ratios of MOM-Cl to imidazole of 4:1 or higher (entries 3-7). The reaction of **169** with

**Table 2.6**. MOM protection of **169** using imidazole.[a]




**169** **170**

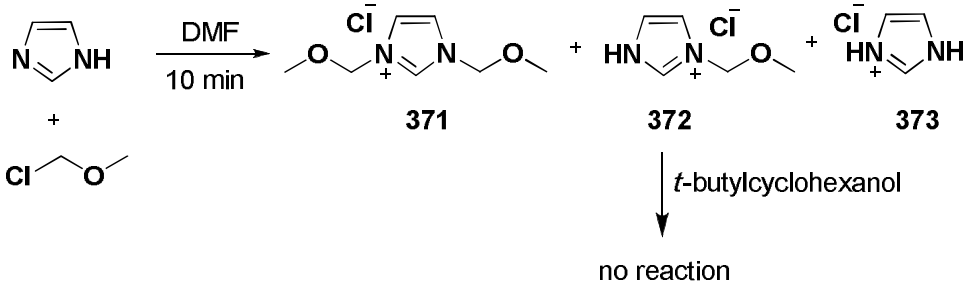
| | MOM-Cl (equiv.) | Imidazole (equiv.) | Time (h) | Ratio[b] (169:170) |
|---|---|---|---|---|
| 1 | 5 | 5 | 20 | 100:0 |
| 2 | 5 | 7 | 20 | 100:0 |
| 3 | 6 | 5 | 20 | 95:05 |
| 4 | 6 | 3 | 20 | 39:61 |
| 5 | 6 | 1.5 | 20 | 12:88 |
| 6 | 5 | 1 | 20 | 14:86 |
| 7 | 5 | 0.5 | 20 | 15:85 |
| 8 | 5 | 1 | 6 | 68:32 |
| 9 | 5 | 1 | 12 | 34:66 |
| 10 | 5 | 1 | 48 | 6:94 |
| 11 | 5 | 0.5 + 0.5[c] | 48 | 2:98 (55%)[d] |

[a] Reaction in DMF (0.25M in **169**) at room temperature.
[b] Ratio determined by $^1$H NMR of the crude product after aqueous work up.
[c] 0.5 equiv. added after 24 h.
[d] Isolated yield of **170**.

MOM-Cl (5 equiv.) and imidazole (1 equiv.) was complete in 48 h (entries 8-10) and gave optimal conversion when the imidazole was added in two portions (entry 11). Surprisingly, although the $^1$H NMR spectrum of the crude product after work up was clean and indicated that full conversion to **170** was achieved; the isolated yield of **170** after chromatography was only 55%. This suggested that the product **170** and/or starting **169** were converted into unknown water soluble compounds under the reaction conditions and lost upon work up.

To further investigate the lack of reactivity under Sardina's conditions, the reaction of MOM-Cl with imidazole in DMF-$d_7$ was monitored by $^1$H NMR. Within 10 min, an equimolar mixture of MOM-Cl and imidazole was converted into an ca. 2:1:2 mixture of **371**, **372** and **373** respectively (Scheme 2.15). With >2 equiv. of MOM-Cl a similar mixture was produced that, over time (72 h), was slowly converted to mainly **371** (>85%). With 2 equiv. of imidazole, a 1.7:1 of **371** and **372** was formed. This mixture was stable over 48 h and importantly, did not react with *t*-butylcyclohexanol even after 48 h.

**Scheme 2.15**. Reaction of imidazole with MOM-Cl in DMF-$d_7$.

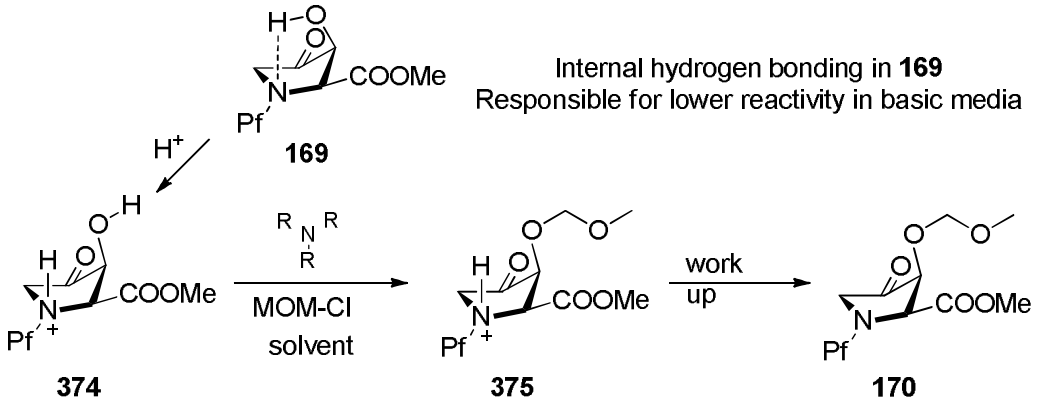



The above experiments explain the results in Table 2.6 and the absence of reactivity under Sardina's conditions. Imidazole rapidly consumes 1 equiv. of MOM-Cl

and, over time, can consume 2 equiv. of MOM-Cl. The products **371** and **372** are not sufficiently reactive to alkylate an alcohol. Thus, using an excess of imidazole or with equimolar imidazole and MOM-Cl (i.e. Sardina's conditions), alkylation of alcohols does not occur (or is exceedingly slow). Using excess MOM-Cl, alkylation is possible but greater than 2 equiv. of MOM-Cl (relative to imidazole) is required for significant conversion. Under these conditions, the alkylation is not mediated by imidazole and the reaction mixture is highly acidic. This aspect can explain the low yields of **170** obtained under these conditions.

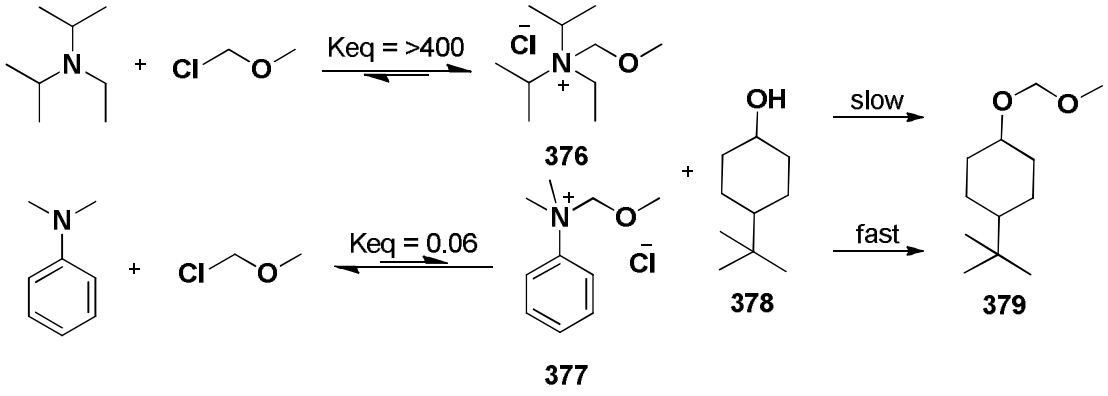
Due to the low amounts of **170** obtained by using MOM-Cl/imidazole, focus was directed on other methods for MOM protection. Along these lines compound **169** was subjected to the standard method for MOM protection using DIPEA and MOM-Cl; the reaction was slow and incomplete, and gave **170** in ca. 50% yield after 3 days. A possible hypothesis for the low reactivity in the basic media is the presence of an internal hydrogen bond that attenuates the nucleophilicity of the hydroxy group in **169** (Scheme 2.16).[150]

**Scheme 2.16.** Hypothesis for MOM ether formation of **169**.



Thus, the reactivity of **169** was apparently lower in basic medium [MOM-Cl (5 equiv.)/DIPEA (7 equiv.)] than in acidic medium [MOM-Cl (5 equiv.)/imidazole (1 equiv.)]. Based on this observation it was hypothesized that the use of a weak tertiary amine base would allow reaction with a protonated **169** to give the desired product with improved reactivity (Scheme 2.16). *N*,*N*-dimethylaniline (DMA) (pKa of protonated DMA = 5.15) was chosen as a base to carry out the MOM protection. Reactions carried out in NMR tubes using MOM-Cl and *N*,*N*-dimethylaniline or DIPEA (pKa of protonated DIPEA = 10.5) revealed that methoxymethyl adducts are rapidly formed with both bases. It was noted that the adduct formation was much more favorable with DIPEA (K*eq*. > 400) compared to DMA (K*eq*. ca. 0.06). Under both conditions, alkylation of *t*-butylcyclohexanol (**378**) to give **379** was facile (100% conversion by $^1$H NMR) although the reaction using DMA was considerably faster than that using DIPEA (Scheme 2.17).

**Scheme 2.17**. NMR tube reactions of MOM-Cl with DIPEA and *N*,*N*-dimethylaninline.

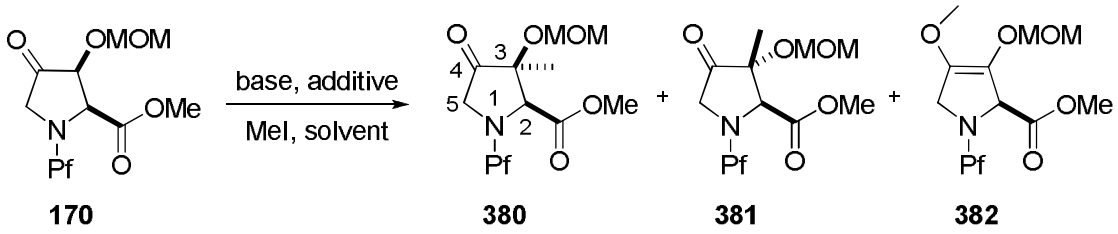



Applying the above results, alcohol **169** was treated with 7 equiv. of *N*,*N*-dimethylaniline and 5 eq. of MOM-Cl in DMF at a concentration of 0.25 M with respect to **169**. After one day, the reaction gave 65% of **170** along with 30% of starting material. The reaction showed similar conversion even after 2 days. Changing the solvent from

DMF to $CH_2Cl_2$ resulted in improved conversions and 80% isolated product of **170** was obtained after 1 day.

The next step was the methylation of ketone **170**. Again, Sardina has reported this reaction using *n*-BuLi in the presence of HMPA at -78 °C to form the enolate and then reaction with MeI at -78 °C to 0 °C giving >60% yield of desired product **380** with no report of any side product.[62] In our hands, repetition of this chemistry under the same reaction conditions as described by Sardina proved very capricious.

**Scheme 2.18.** Alkylation of **170**.



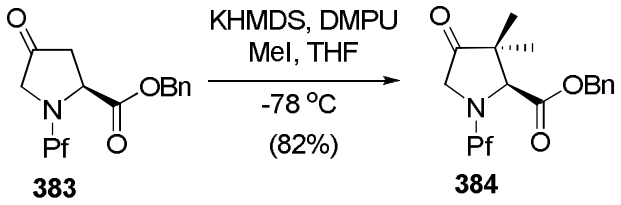

**170** **380** **381** **382**

Enolization experiments of ketone **170** with *n*-BuLi and HMPA followed by quenching with $D_2O$ showed that enolate formation was essentially quantitative under the reported conditions. However, upon warming up to 0 °C, the enolate decomposed. It was determined that the enolate was stable below -50 °C. Several reaction parameters including time, temperature, solvent, and additives were studied, but no significant improvement was noted. However, when the reaction was carried out at -50 °C, 35% of **380**, accompanied by several other side products (the C-3 diastereomer **381**, the *O*-alkylation product **382,** etc.) were observed. Unfortunately, the formation of side products could not be suppressed even after extensive experimentation.

Lubell and co-workers[151] have reported the alkylation of a 4-oxoproline derivative (**383**) after generating the enolate using KHMDS and DMPU in THF (Scheme 2.19). The

Lubell protocol was optimized for the methylation of **170**. Quantitative enolate formation from **170** using KHMDS as base at -78 $^{o}$C was demonstrated by quenching with $D_2O$ and obtaining >95% deuterium incorporation at C-3. Toluene was found to be the best solvent

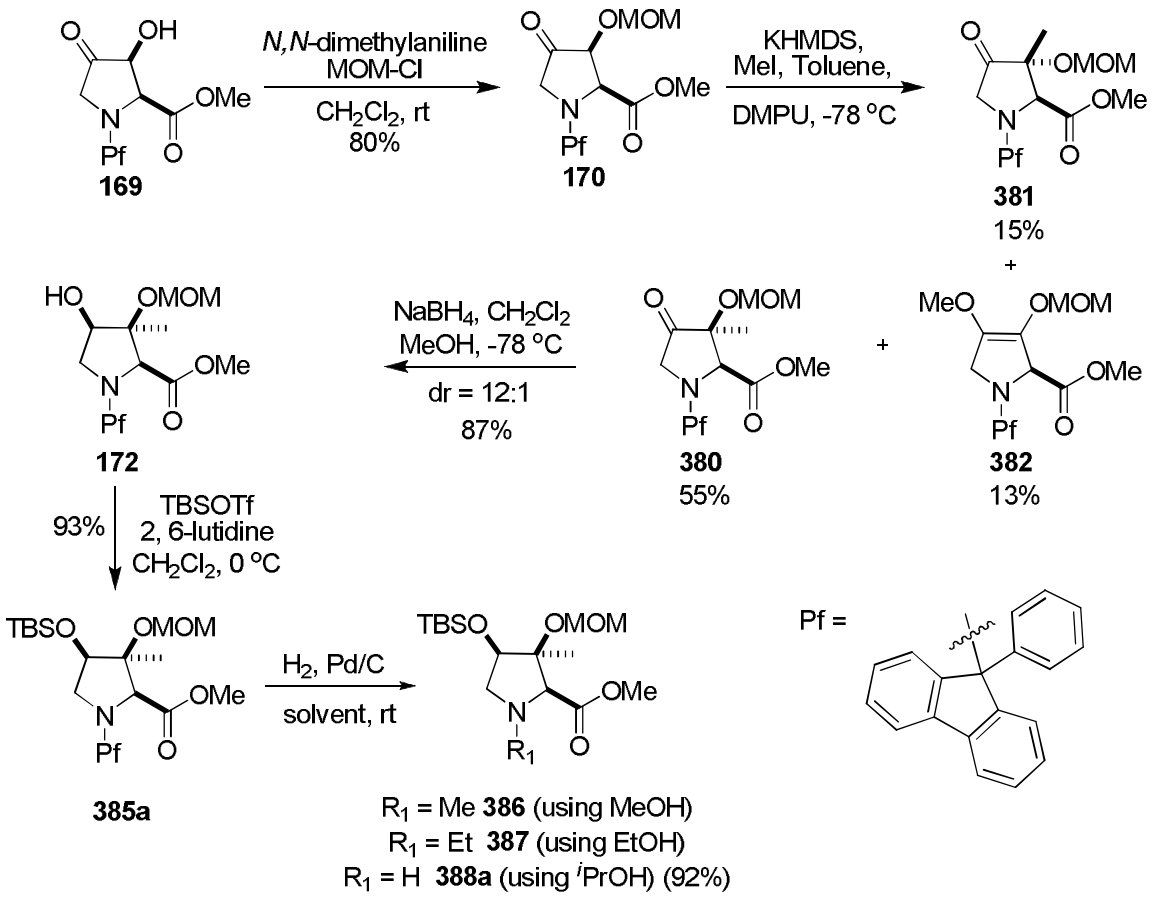
**Scheme 2.19.** Alkylation of 4-oxoproline **383** using KHMDS by Lubell *et al*.




and showed cleaner reactions while DMPU was found to be the best additive (HMPA and TMEDA showed poor or no reaction). A minimum amount of side products were seen when 1.05 equiv. of KHMDS with toluene–DMPU (1:1) as solvent were used at -78 °C. Under optimized conditions, 55% of the desired **380** was obtained along with 15% of the C-3 diastereomer **381** and 13% of the *O*-methylated product **382** (Scheme 2.20).

Reduction of ketone 380 using $NaBH_4$ gave the desired alcohol 172, which was subsequently protected as its TBS ether 385a (Scheme 2.20). Hydrogenolysis of compound 385a using MeOH or EtOH as a solvent gave the desired 388a along with various amounts of corresponding *N*-methylated (386) or *N*-ethylated amine (387). These byproducts presumably result from reductive amination by the aldehydes formed by oxidation of MeOH or EtOH to corresponding aldehyde perhaps mediated by Pd(II)

**Scheme 2.20**. Synthesis of protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline.

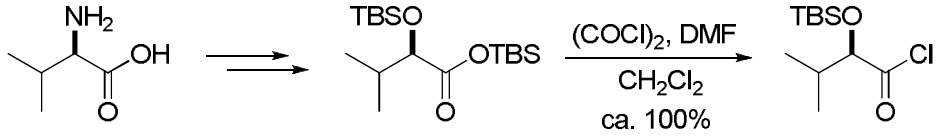



contaminants in the catalyst. The oxidation of the alcohols by molecular oxygen in the presence of Pd (II) is known.[152] The aldehyde formed in situ can react with the deprotected amine to form the iminium ion which upon reduction in the presence of $H_2$ and Pd/C can afford the corresponding *N*-alkylated products. However, side product formation could be completely avoided by the use of $^{i}$PrOH for the hydrogenolysis which gave the desired proline fragment **388a** in its fully protected form in excellent yield (Scheme 2.20).

### 2.2.4 Synthesis of protected hydroxy valeric acid chloride (390)

Commercially available D-valine (*ent*-**59**) was transformed into silyl-ether-ester **389** in good yield by using a known procedure.[85, 86] Compound **389** was treated with oxalyl chloride and catalytic DMF to give hydroxy valeric acid chloride **390**, poised for facile amide bond formation[24] (Scheme 2.21).

**Scheme 2.21**. Synthesis of protected hydroxy valeric acid chloride.

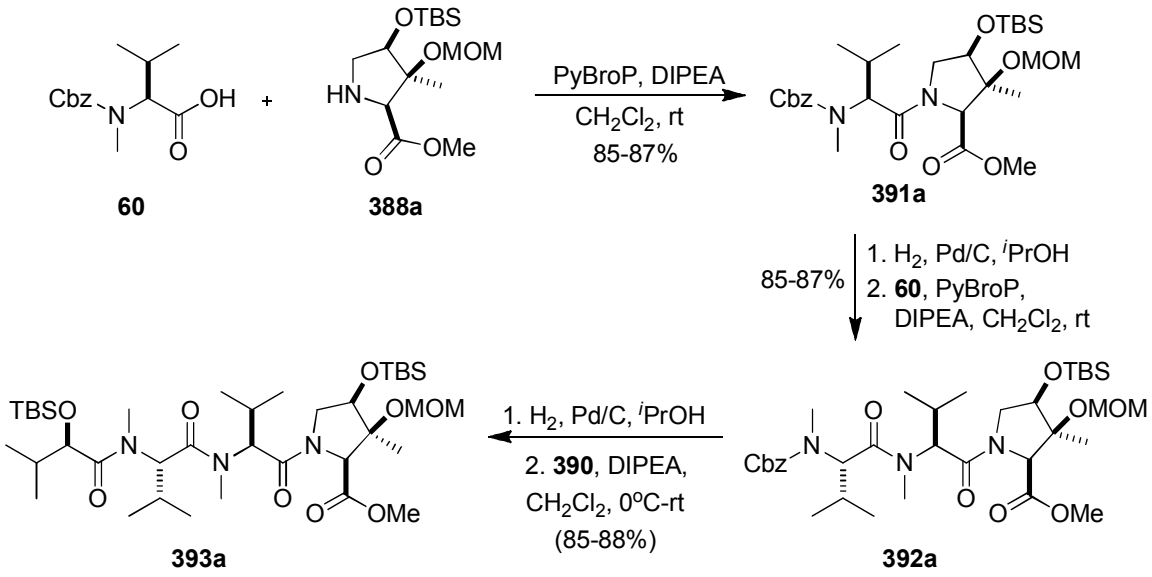



*ent*-**59** **389** **390**

### 2.2.5 Assembly of the fragments

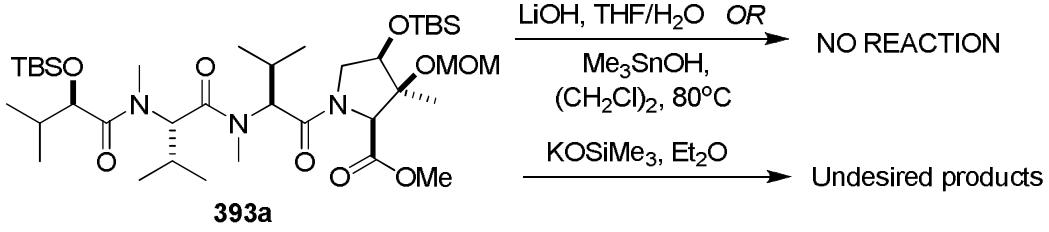
As stated in the retrosynthetic analysis (section 2.2.1), synthesis of the desired tetrapeptide fragment was pursued via the *N*-terminal extension due to its lower tendency for racemization. Proline **388a** was coupled with Cbz-*N*-Me-Val (**60**)[83] using PyBroP[153, 154] to give **391a** in good yield (Scheme 2.22). PyBroP was chosen as a coupling agent because it is specially designed for the coupling of hindered amino acids such as *N*-Me-Val and proline.[153, 154] Cbz deprotection of **391a** followed by PyBroP mediated coupling with another unit of **60**[83] furnished **392a**. Tripeptide **392a** was then subjected to hydrogenolysis followed by reaction with the TBS protected hydroxy valeric acid chloride **390**, which gave the desired tetrapeptide **393a** in excellent yield. All the peptide coupling reactions occurred with negligible epimerization (Scheme 2.22), as determined by $^1$H NMR analysis.

**Scheme 2.22**. Synthesis of tetrapeptide **393a** towards depsilairdin.




The next step was to esterify lairdinol A (**51**) with the carboxylic acid corresponding to **393a**. Unfortunately, when the tetrapeptide **393a** was subjected to treatment with LiOH in $H_2O$/THF or $Me_3SnOH$[155] in 1,2-dichloroethane or $KOSiMe_3$ in $Et_2O$, only starting material and/or undesired products were recovered. This result was attributed to steric hindrance of the methyl ester group in tetrapeptide **393a**.

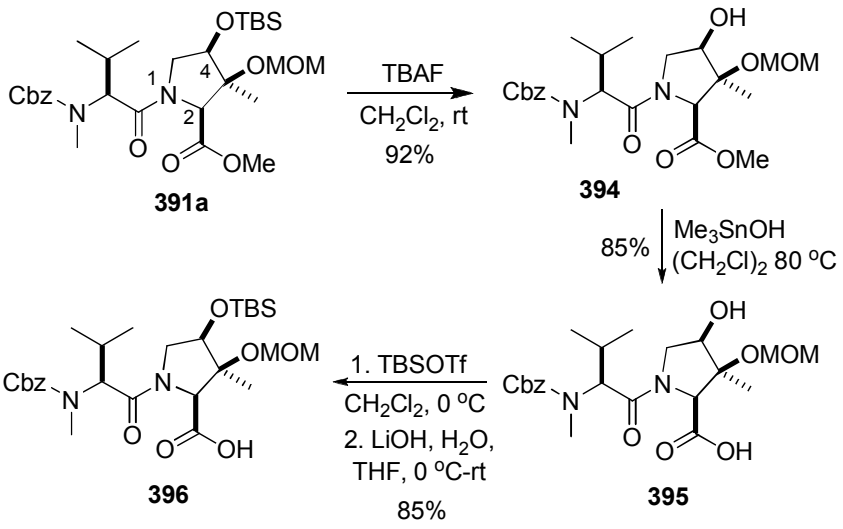
**Scheme 2.23.** Attempted hydrolysis of (**393a**).



### 2.2.6 Model studies towards the hydrolysis of 393a

Due to the failure to hydrolyze the methyl ester in **393a**, dipeptide **391a** was chosen as a model to study the hydrolysis. The two compounds have the same functionality and only differ in the peptide chain. As expected, attempted hydrolysis of **391a** using LiOH in THF/$H_2O$ at room temperature or using $Me_3SnOH$[155] in $(CH_2Cl)_2$ showed no reaction. At this stage it was hypothesized that the deprotection of the TBS group on the $2^o$ alcohol in the proline moiety would reveal a hydroxy group might assist the hydrolysis by activating the carbonyl group by H-bonding or by an initial trans esterification to a more labile lactone. Thus, TBS deprotection in **391a** was achieved by treatment with TBAF to obtain **394**. Gratifyingly, the hydrolysis of **394** with $Me_3SnOH$[155] gave the desired acid **395** in good yield. Thus, the deprotection studies on **391a** clearly revealed that the hydrolysis of the methyl ester can be accomplished if the alcohol group at C-4 position in **391a** is unprotected. Subsequent TBS protection of the secondary alcohol in **395** afforded **396** in good yield after hydrolysis of the intermediate TBS-ester (Scheme 2.24).

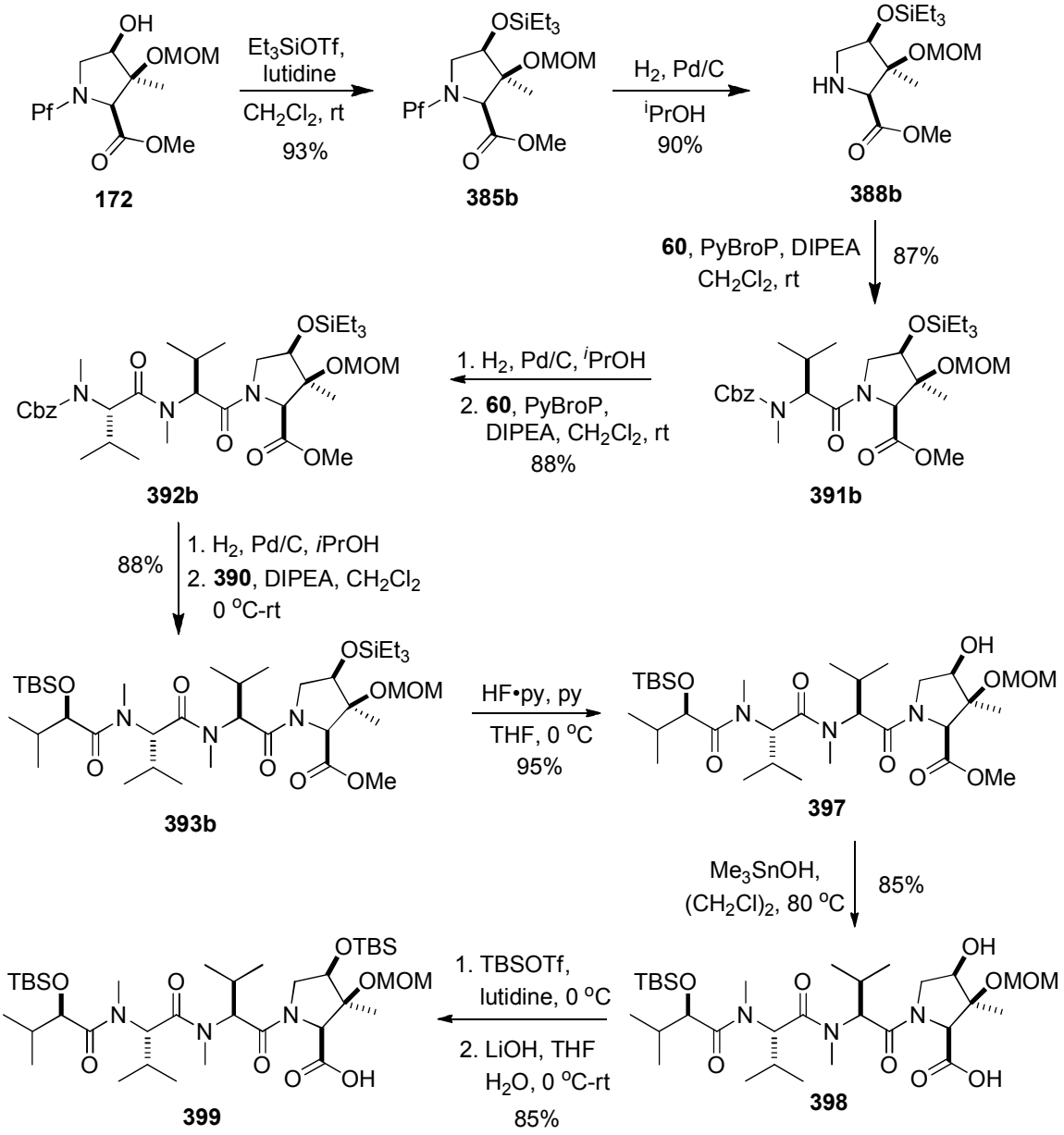
**Scheme 2.24**. Hydrolysis study of dipeptide **391a**.




## 2.2.7 Synthesis of the tetrapeptide acid 399

After the successful hydrolysis of dipeptide **391a**, it was decided to prepare a differentially protected tetrapeptide fragment where the 2$^{o}$ alcohol in the proline fragment could be selectively deprotected to give the corresponding tetrapeptide alcohol, thereby facilitating ester hydrolysis using $Me_3SnOH$. In this regard, alcohol **172** was protected as its TES ether to afford compound **385b** in excellent yield (Scheme 2.25). Hydrogenolysis of **385b** using $H_2$, Pd/C in $^{i}$PrOH gave the desired TES-protected proline **388b** which was converted to the desired differentially protected tetrapeptide fragment **393b** following the same protocol as for the synthesis of **393a**. The triethylsilyl group in **393b** was selectively removed using HF·pyridine in pyridine to obtain **397**. Alcohol **397** was subjected to ester hydrolysis using Nicolaou's protocol and, as expected, gave acid **398** in 85% yield. TBS protection of **398** followed by hydrolysis of the intermediate TBS-ester gave acid **399** in high yield (Scheme 2.25).

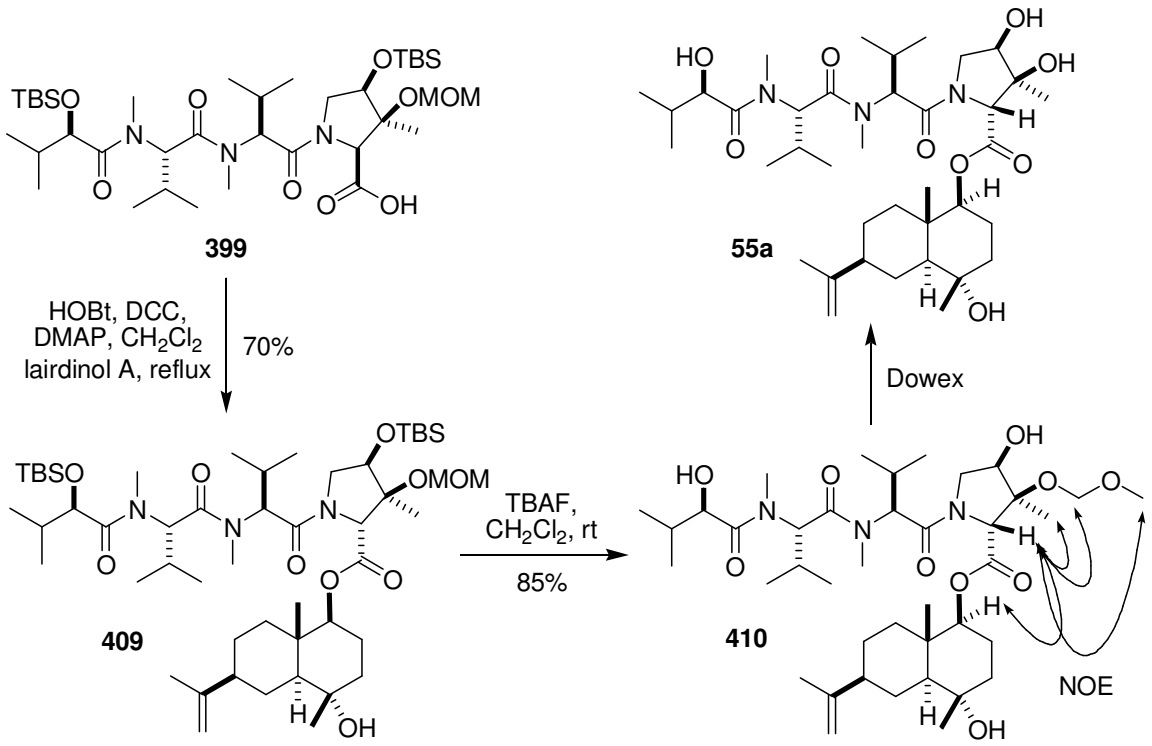
**Scheme 2.25**. Synthesis of tetrapeptide acid **399**.



### 2.2.8 Esterification studies of acid 396

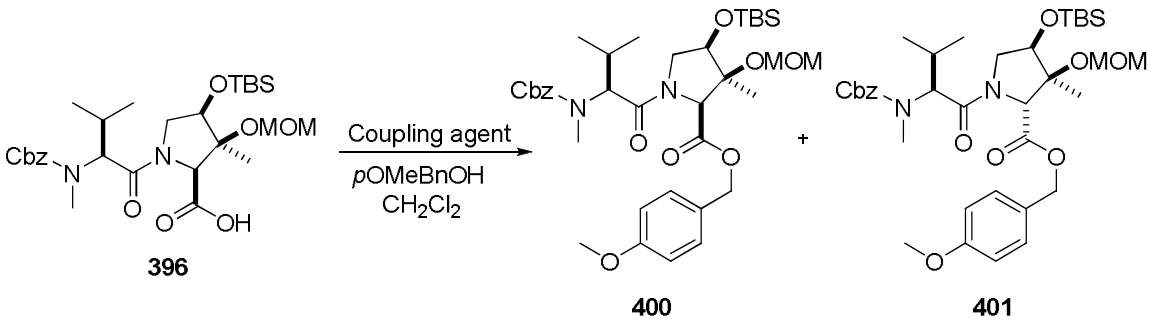
Given the difficulties experienced in the hydrolysis of the methyl ester in **393a**, it was anticipated that esterification of the hindered acid in **399** with the hindered secondary –OH group in lairdinol A (**51**) might prove challenging. Surprisingly, the reaction of acid **399** with lairdinol A using DCC/DMAP mediated coupling in the presence of HOBt gave the ester **409** in 70% yield (Scheme 2.26). However, removal of the TBS and MOM ethers in **409** by sequential treatment with TBAF and Dowex gave compound **55a** that was clearly different from depsilairdin (**55**) by $^{1}H$ and $^{13}C$ NMR. Careful analysis of the spectroscopic data for the precursor **410**, particularly using NOE, showed that the esterification had occurred with isomerization at the proline C-2 position. In light of the above result, a more detailed examination of the desired esterification reaction was warranted.

**Scheme 2.26.** DCC-HOBt/DMAP mediated esterification of **399**.



Compound **396** was thought to be a perfect model for studying the esterification of the desired tetrapeptide acid **399**. Esterification of acid **396** with *p*-OMeBnOH using different coupling agents such as DCC/DMAP, EDCI and PyBroP gave the desired ester **400** along with the diastereomer **401** (For product distribution see Table 2.7). At this stage, it was clear that the esterification reactions were slow and accompanied with isomerization. An alternative plan was to generate thiopyridyl (active) ester[156] **402** and test it for esterification. Esterification of **402** with *p*-OMeBnOH using Nicolaou's protocol[105] (Δ, toluene) gave isomerized product **401** in quantitative yields. The reaction presumably occurred via the corresponding ketene (**403**) followed by selective protonation after the addition of alcohol. When the putative bromomagnesium alkoxide prepared by reaction of *p*-OMeBnOH with MeMgBr was used as the nucleophile, the desired ester was obtained in good yield.

**Table 2.7**. Product ratio during esterification of **396**.

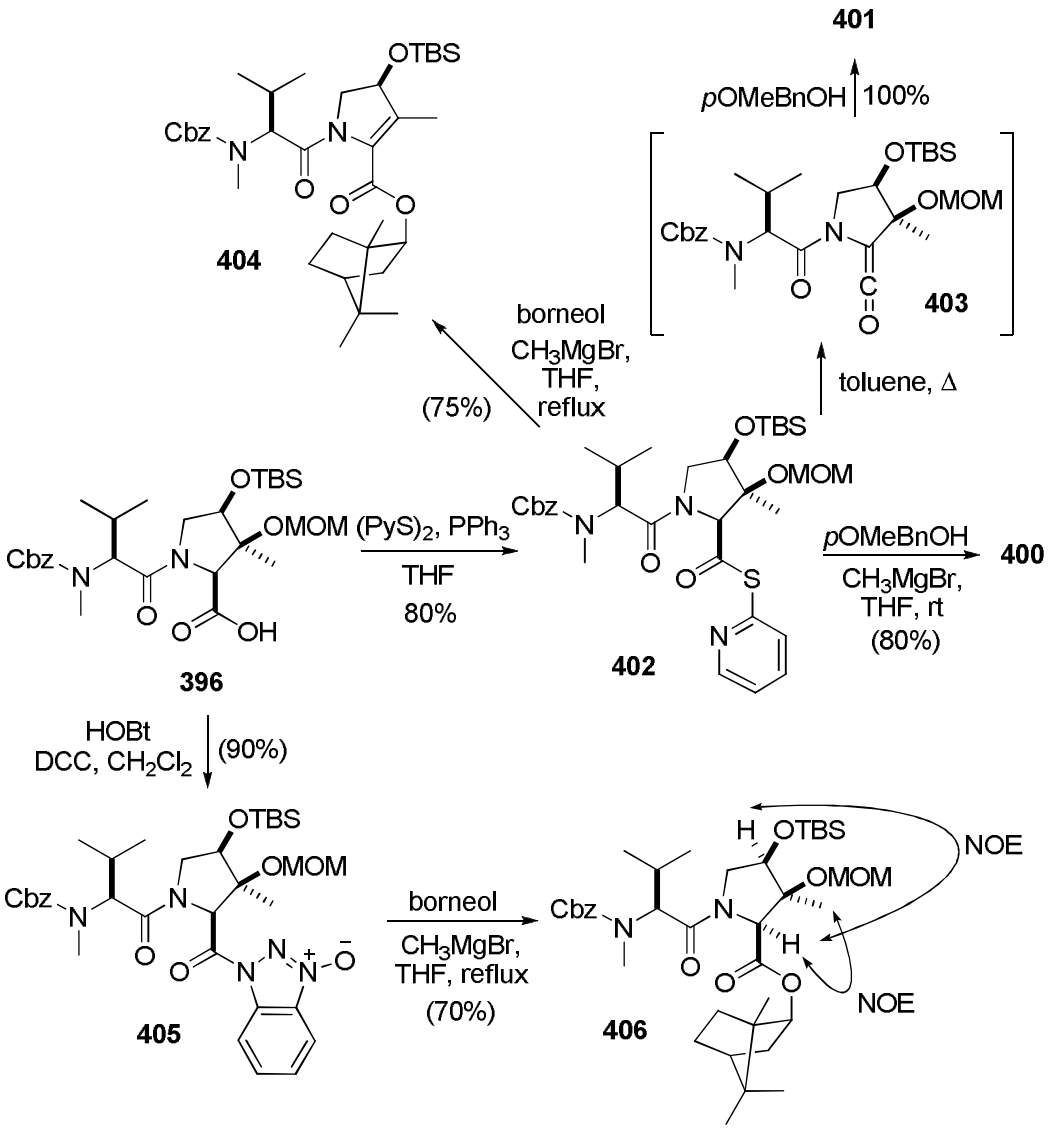



396 400 401

| Coupling Agent | Product Ratio[a] (400 : 401) |
|---|---|
| DCC/DMAP | 70 : 30 |
| EDCI·HCl | 50 : 50 |
| PyBroP | 45 : 55 |

[a] Ratio determined by $^1$H NMR.

**Scheme 2.26**. Esterification of thiopyridyl ester **402** and HOBt ester **405**.




Interestingly, an analogous reaction of **402** with the Li alkoxide (prepared by reaction of *p*-OMeBnOH with BuLi) gave only the isomerized product **401** even at low conversion. As lairdinol A (**51**) has a hindered secondary alcohol, it was decided to carry out the esterification of **402** with the hindered secondary alcohol borneol to test and optimize reaction conditions for the esterification of **399** with lairdinol A. Reaction of the bromomagnesium alkoxide of borneol with **402** at room temperature showed no

conversion, while the elimination product **404** was observed under refluxing conditions (Scheme 2.27).

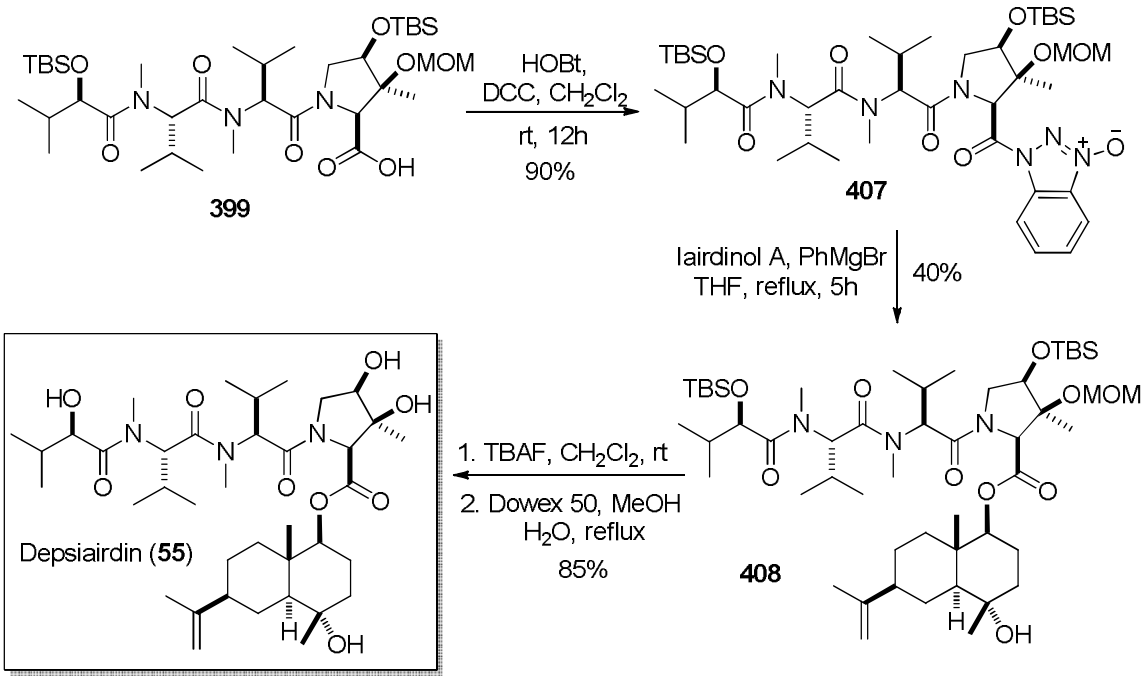
In an effort to suppress the tendency for isomerization, elimination, and ketene formation, it was decided to use activated esters with lower acidity at the α-CH. In this regard, HOBt esters have been very successful in peptide coupling applications. In the first attempt, the HOBt ester[99] **405** was easily prepared and subjected to esterification by reaction with the bromomagnesium alkoxide of borneol to afford the desired borneol ester **406** in good yield (Scheme 2.27).[†] Thus, the esterification of **405** with borneol was feasible and these conditions were applied toward the synthesis of depsilairdin (**55**). The HOBt ester of **399** was readily prepared (Scheme 2.28). Initial attempts to effect esterification of the resulting **407** using the bromomagnesium alkoxide of lairdinol A (prepared by the reaction of $CH_3MgBr$ with lairdinol A) gave **408** in ca. 30% yield along with undesired side products when a large excess of lairdinol A (10 equiv.) and $CH_3MgBr$ (5 equiv.) were used. Using less lairdinol A (2 equiv.) along with $CH_3MgBr$ (2 equiv.) produced a significant amount of **393a** (ca 40%), presumably due to the presence of $CH_3OMgBr$ resulting from oxidation of $CH_3MgBr$ in the presence of oxygen.[107] Using freshly prepared PhMgBr (2 equiv.) in place of $CH_3MgBr$ under the same conditions gave 40% of **408** (20% based on lairdinol A) along with recovered lairdinol A (75%).

[†] The relative configuration was determined by NOE.

### 2.2.9 Endgame

With ester **408** in hand, only final deprotection was required to reach depsilairdin (**55**). Reaction of **408** with TBAF in $CH_2Cl_2$ effected removal of the two TBS ethers and, without purification of the resulting diol, treatment with Dowex 50 in refluxing aqueous MeOH[157] gave depsilairdin (**55**) in good yield (Scheme 2.28).

**Scheme 2.27**. Endgame of depsilairdin (**55**).




$^1H$ and $^{13}C$ NMR spectra in $CDCl_3$ for synthetic **55** were essentially superimposable with those for natural **55** kindly provided by Prof. Pedras. Specific rotation for synthetic **55** was obtained in $CH_2Cl_2$ [-45 (*c* 0.15, $CH_2Cl_2$)] and was comparable with the reported value [-65 (c 0.90, $CH_2Cl_2$)].[25] The $^1H$ NMR and $^{13}C$ NMR

data (obtained in $CDCl_3$) for natural and synthetic depsilairdin (**55**) are summarized below (Table 2.8).

**Table 2.8.** Comparison of spectral data of synthetic and natural depsilairdin (**55**).

| **Natural depsilairdin ($CDCl_3$)** $[\alpha]_D$ = -65 (*c* 0.9, $CH_2Cl_2$)[a] | | **Synthetic depsilairdin ($CDCl_3$)** $[\alpha]_D$ = -45 (*c* 0.15, $CH_2Cl_2$) | |
|---|---|---|---|
| **$^1$H NMR** | **$^{13}$C NMR** | **$^1$H NMR** | **$^{13}$C NMR** |
| 5.12 (1H, d, *J* = 11 Hz) | 175.0 | 5.13 (1H, d, *J* = 11 Hz) | 175.0 |
| 4.98 (1H, d, J = 11 Hz | 171.8 | 4.99 (1H, d, J = 11 Hz | 172.1 |
| 4.69 (2H, br s) | 171.3 | 4.70 (2H, br s) | 171.3 |
| 4.67 (1H, dd, J = 4, 12 Hz) | 170.3 | 4.67 (1H, dd, J = 4, 12 Hz) | 170.4 |
| 4.24-4.28 (2H, m) | 150.4 | 4.29-4.25 (2H, m) | 150.4 |
| 4.23 (1H, dd, J = 5, 11.5 Hz) | 108.6 | 4.24 (1H, dd, J = 5, 11.5 Hz) | 108.7 |
| 3.83-3.75 (2H, m) | 83.5 | 3.84-3.78 (1H, m) | 83.6 |
| | 76.6 | 3.77-3.72 (1H, m) | 76.71 |
| 3.45 (1H, br s) | 76.5 | 3.43 (1H, d, J = 7.5) | 76.67 |
| 3.14 (3H, s) | 72.8 | 3.15 (3H, s) | 72.9 |
| 2.97 (3H, s) | 71.5 | 2.98 (3H, s) | 71.5 |
| 2.38-2.30 (1H, m) | 67.4 | 2.39-2.31 (1H, m) | 67.5 |
| 2.30-2.23 (1H, m) | 59.2 | 2.31-2.23 (1H, m) | 59.3 |
| 1.96-1.86 (3H, m) | 58.9 | 1.95-1.87 (3H, m) | 58.9 |
| 1.86-1.74 (6H, m) | 53.4 | 1.87-1.84 (3H, m) | 53.5 |
| | 53.0 | 1.84-1.75 (3H, m) | 53.2 |
| 1.73 (3H, s) | 45.7 | 1.73 (3H, s) | 45.8 |
| 1.62-1.52 (3H, m) | 40.7 | 1.65-1.50 (3H, m) | 40.8 |
| 1.37 (3H. s) | 40.4 | 1.37 (3H. s) | 40.5 |
| 1.34-1.20 (2H, m) | 38.3 | 1.30-1.20 (2H, m) | 38.3 |

| | | | |
|---|---|---|---|
| 1.14 (3H, s) | 31.0 | 1.15 (3H, s) | 31.0 |
| 1.09 (3H, d, J = 7) | 30.8 | 1.09 (3H, d, J = 7) | 30.9 |
| 1.00 (3H, s) | 30.1 | 1.00 (3H, s) | 30.1 |
| 0.97 (3H, d, J = 7) | 27.7 | 0.97 (3H, d, J = 7) | 27.7 |
| 0.85 (6H, d, J = 7) | 27.6 | 0.85 (6H, d, J = 7) | 27.6 |
| 0.79 (3H, d, J = 7) | 26.4 | 0.80 (3H, d, J = 7) | 26.5 |
| 0.76 (3H, d, J = 7) | 25.8 | 0.77 (3H, d, J = 7) | 25.9 |
| | 25.3 | | 25.4 |
| | 25.1 | | 25.2 |
| | 22.7 | | 23.0 |
| | 21.3 | | 21.3 |
| | 20.3 | | 20.3 |
| | 19.6 | | 19.6 |
| | 19.2 | | 19.3 |
| | 18.60 | | 18.62 |
| | 18.56 | | 18.59 |
| | 14.7 | | 14.7 |
| | 14.4 | | 14.4 |

[a]Ref. 25

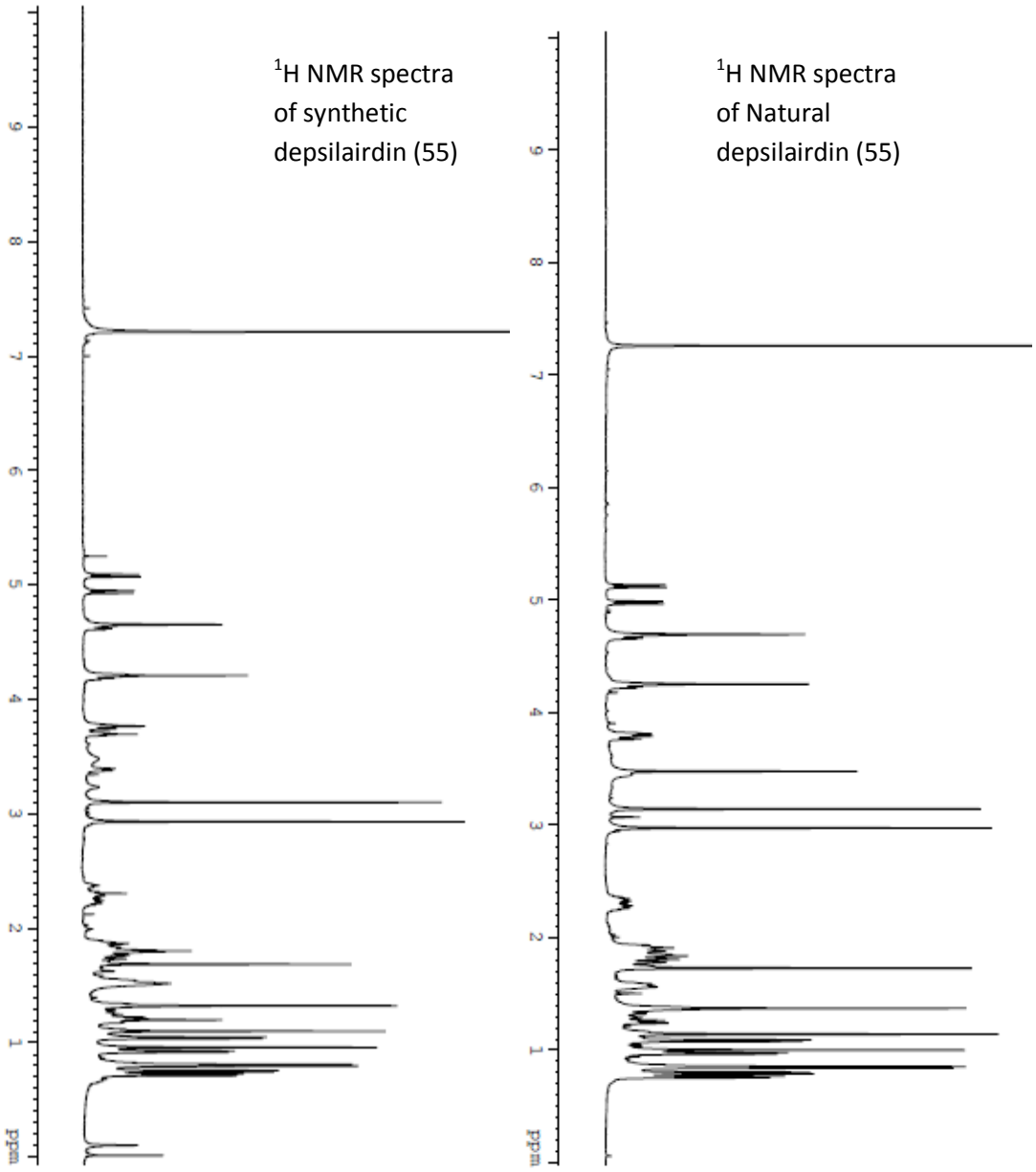



**Figure 2.7**. $^1$H NMR spectras for natural and synthetic depsilairdin (**55**).

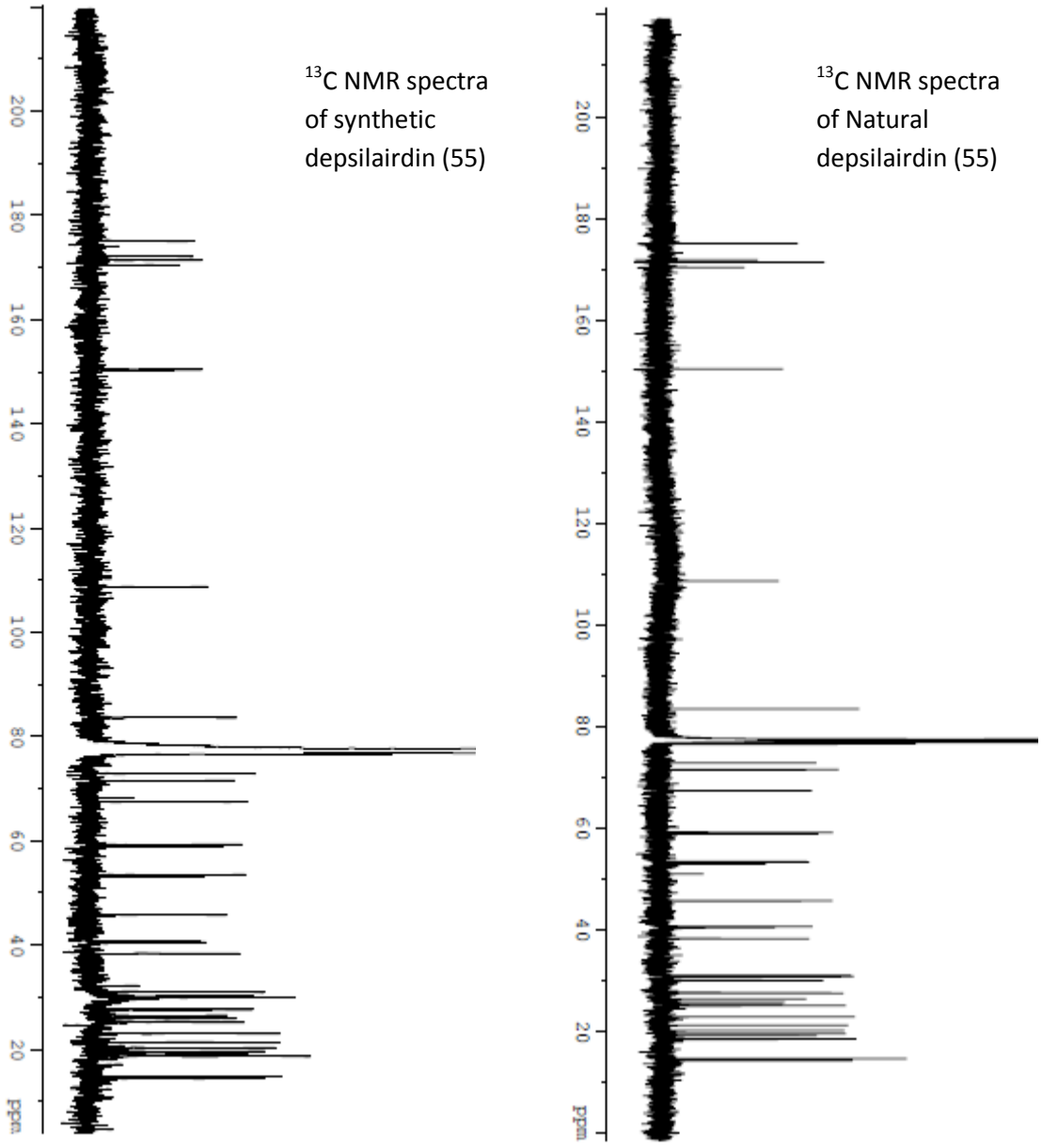


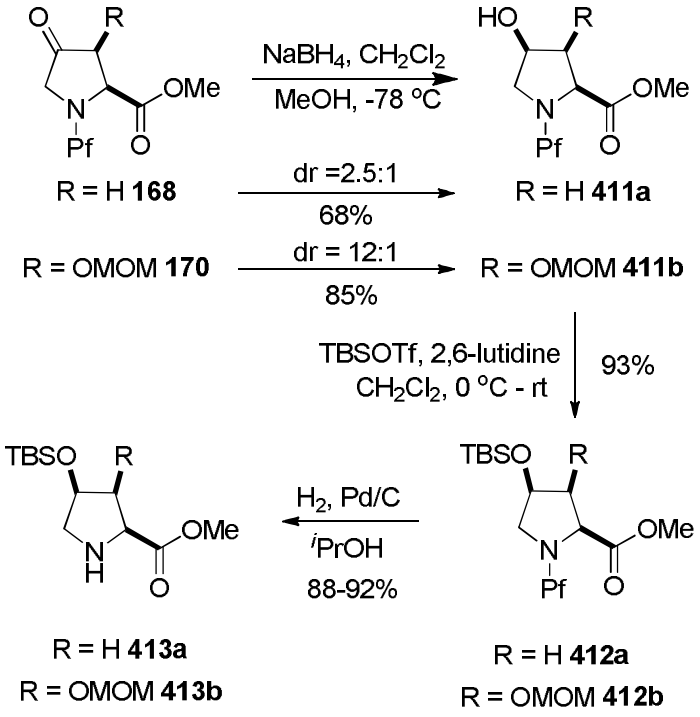

**Figure 2.8**. $^{13}$C NMR spectras for natural and synthetic depsilairdin (**55**).

## 2.3 Synthesis of depsilairdin analogues

### 2.3.1 Synthesis of protected (2*S*,4*S*)-4-hydroxy-L-proline and protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-L-proline

The synthesis of (2*S*,4*S*)-4-hydroxy-L-proline commenced with previously synthesized compound **168**. $NaBH_4$ reduction gave the desired alcohol **411a** in 68% yield along with 28% of the (4*R*)-isomer (dr = 2.5:1). Similar reduction of **170** gave the desired alcohol **411b** in 85% yield (dr = 12:1). Alcohols **411a** and **411b** were protected by reaction with TBSOTf to furnish **412a** and **412b** respectively. Hydrogenolysis of the –Pf group in prolines **412a** and **412b** gave the TBS-protected (2*S*,4*S*)-4-hydroxy-L-proline **413a** and TBS-protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-L-proline **413b**, respectively, in good yields (Scheme 2.29).

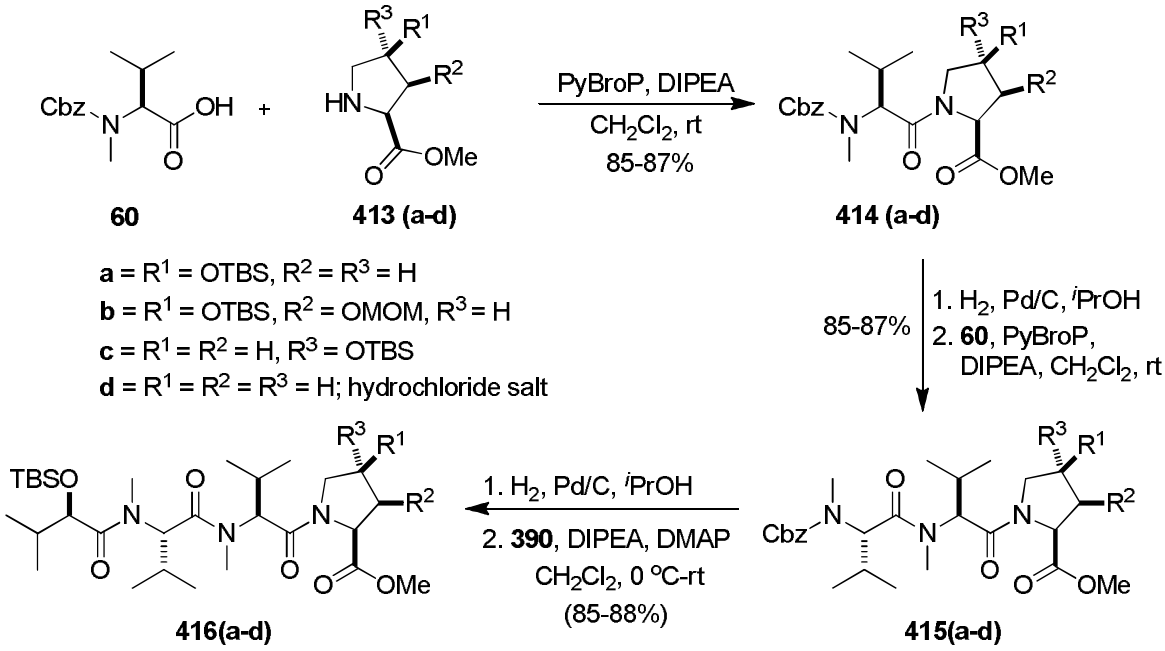
**Scheme 2.28.** Synthesis of protected (2*S*,4*S*)-4-hydroxy-L-proline (**413a**) and protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-L-proline (**413b**).



### 2.3.2 Fragment assembly and endgame

TBS-protected *trans*-4-hydroxy-L-proline methyl ester was prepared by using a known procedure reported by Sames *et al.*[158] Thus, proline analogues **413**(**a**-**d**) were individually coupled with **60**[83] using PyBroP[153, 154] to give **414**(**a**-**d**) in good yields. Cbz deprotection of **414**(**a**-**d**) followed by coupling with **60**[83] furnished **415**(**a**-**d**). Tripeptides **415**(**a**-**d**) were then subjected to hydrogenolysis and coupled with the TBS protected hydroxy valeric acid chloride[24] (**390**) to afford tetrapeptides **416**(**a**-**d**) as sole products in excellent yields (Scheme 2.30).

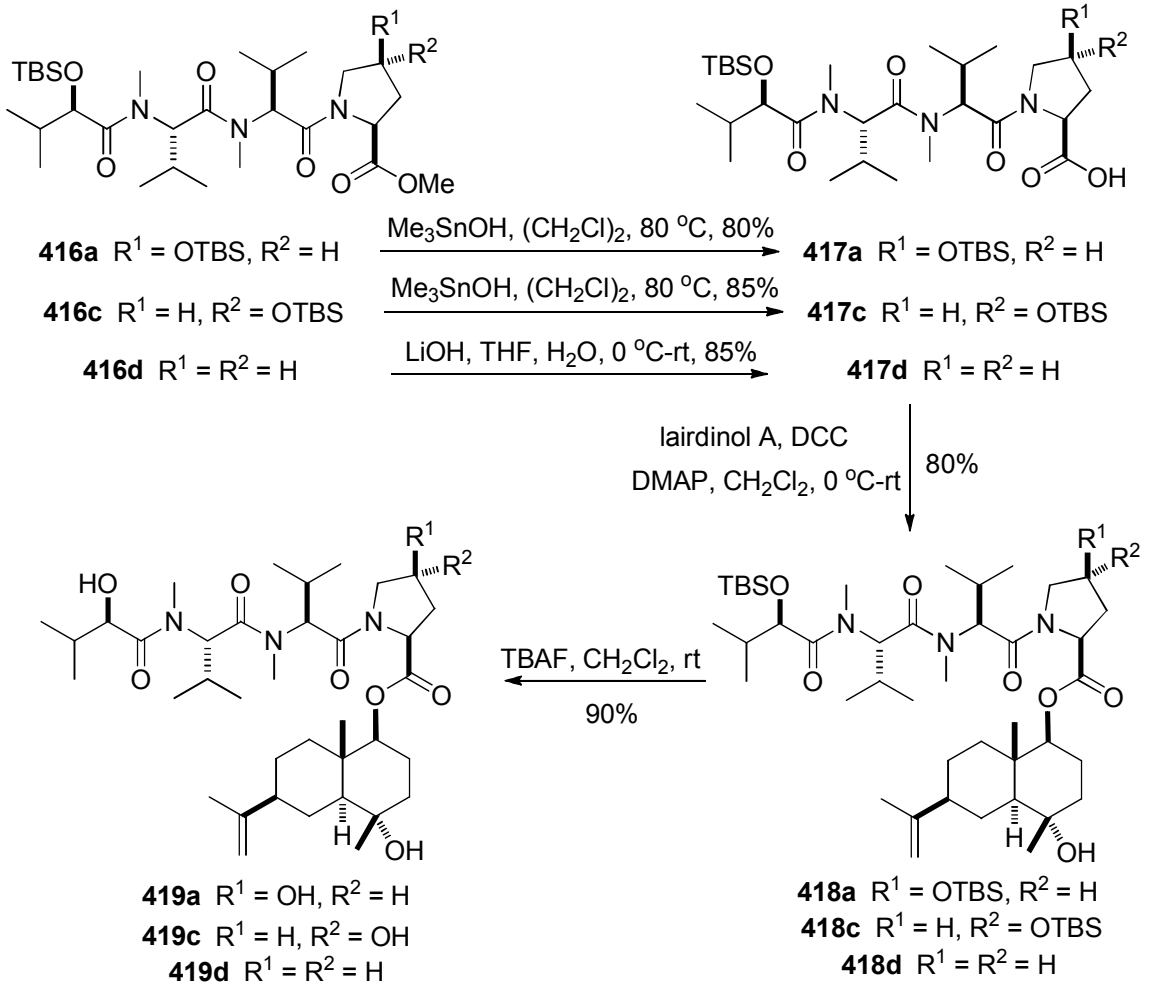
**Scheme 2.30.** Synthesis of tetrapeptides towards depsilairdin analogues.




Hydrolysis of **416d** was successfully achieved using LiOH in THF/$H_2O$ to afford tetrapeptide acid **417d**. Similar hydrolysis of tetrapeptide **416a** gave an acid with only

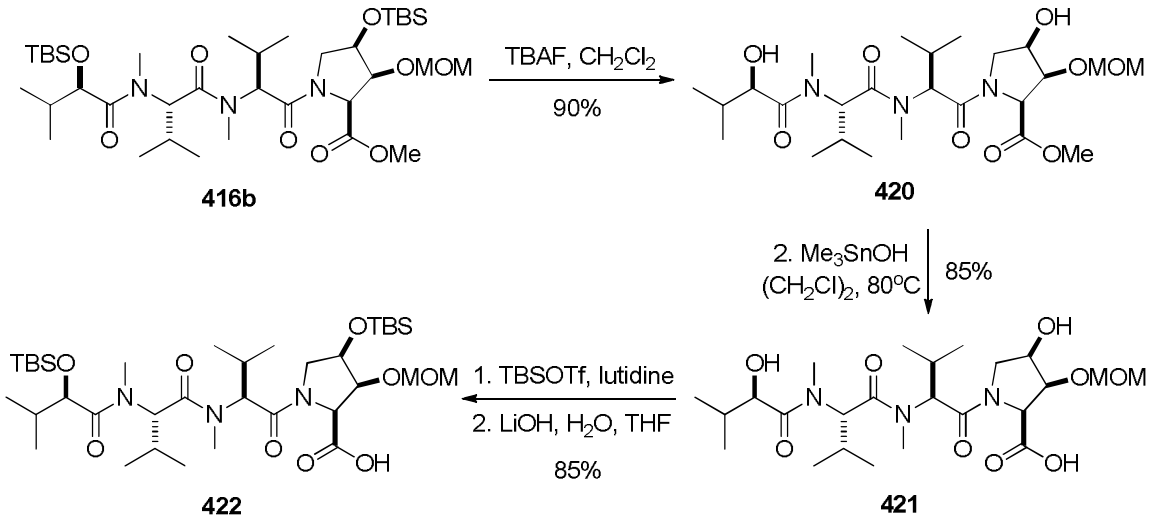
one TBS group. However, when the hydrolysis of **416a** was carried out using $Me_3SnOH$[155] in 1,2-dichloroethane, the anticipated acid **417a** was obtained in good yield. Similar hydrolysis of tetrapeptide **416c** gave the corresponding acid **417c**. The respective acids were subjected to esterification with lairdinol A using DCC/DMAP to furnish the corresponding esters **418a,c,d**. Finally, TBS deprotection of **418a,c,d** using TBAF gave the depsilairdin analogues **419a**, **419c** and **419d** in good yields (Scheme 2.30).

**Scheme 2.29.** Synthesis of L-proline, *cis* and *trans*-4-hydroxy-L-proline analogues.



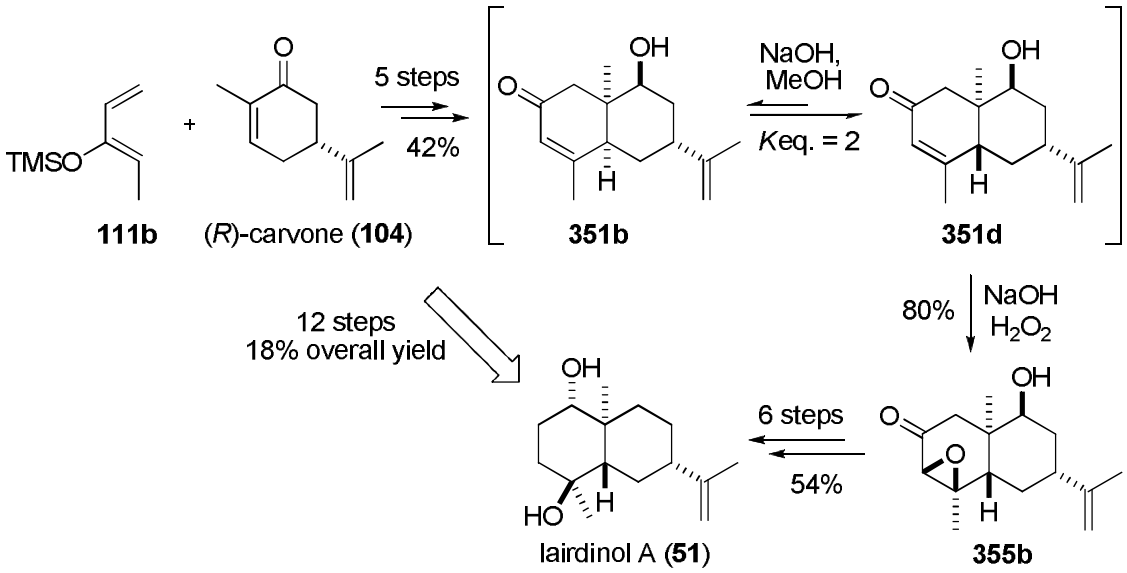
Hydrolysis of the tetrapeptide **416b** was difficult, as was observed with tetrapeptides **393a** and **393b**. Using the same protocol that was successful for the hydrolysis of **393b**, **416b** was subjected to desilylation using TBAF to furnish diol **420**. Subjecting **420** to treatment with $Me_3SnOH$ gave the desired acid which was subsequently protected as its bis-TBS ether to afford the desired acid **422** in high yield after treatment with $LiOH/H_2O$ (Scheme 2.31). Attempted esterification of **422** with DCC/DMAP was not successful. Although the method using the HOBt ester and the bromomagnesium alkoxide of lairdinol A is expected to be suitable in this case, time constraints did not allow that approach to be tested.

**Scheme 2.30.** Synthesis of **422** toward (2*S*,3*S*,4*R*)-3,4-hydroxy-L-proline analogue.



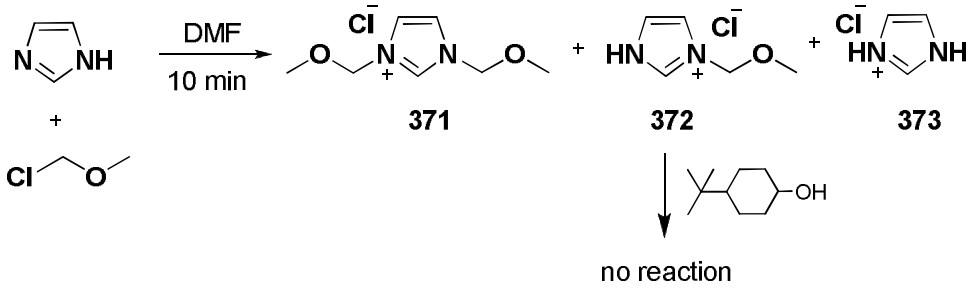
## 2.4 Summary and Conclusions

The synthesis of lairdinol A (**2**) was achieved in 18% overall yield from (*R*)-carvone over 12 steps in the longest linear sequence. Novel features of the synthesis include (i) the construction of the skeleton via a Diels-Alder reaction and (ii) establishment of the trans ring junction by preferential epoxidation of a trans enone in an equilibrating mixture of the cis and trans diastereomers, an example of (type III) dynamic kinetic asymmetric transformation (DYKAT). It is also noteworthy that the entire synthesis proceeded without the use of protecting groups. This preparation is the first reported total synthesis of lairdinol A and it confirmed the absolute configurations of lairdinol A and its enantiomer, cyperusol C.

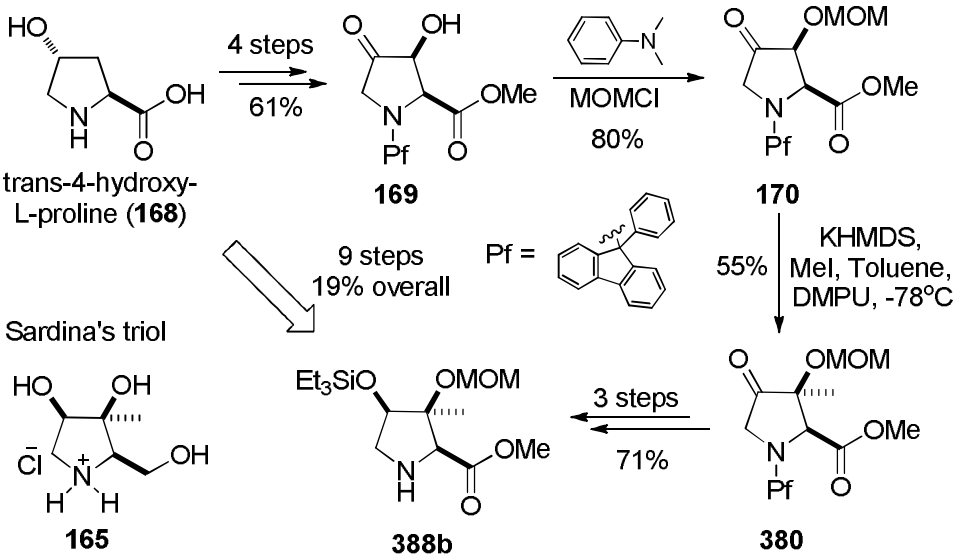



The synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline was not known and a successful route was achieved using Sardina's synthesis of triol (**58**) as a guide. However, the synthesis required serious optimizations during the MOM protection and enolate alkylation steps. It was shown that the MOM protection using Sardina's conditions (5 equiv. MOM-Cl and 5 equiv. imidazole in DMF) is not feasible. NMR tube

experiments showed the formation ca. 2:1:2 mixture of **371**, **372** and **373** respectively when an equimolar mixture of MOM-Cl and imidazole was used. With >2 equiv of MOM-Cl, a similar mixture was produced that, over time (72 h), was slowly converted to mainly **371** (>85%). When imidazole was used in excess (2 equiv.), a 1.7:1 of **371** and **372** was formed, which was stable over 48 h and did not show any reaction with *t*-butylcyclohexanol even after 2 days. The MOM protection was best achieved by using MOM-Cl and *N*,*N*-dimethylaniline as base.



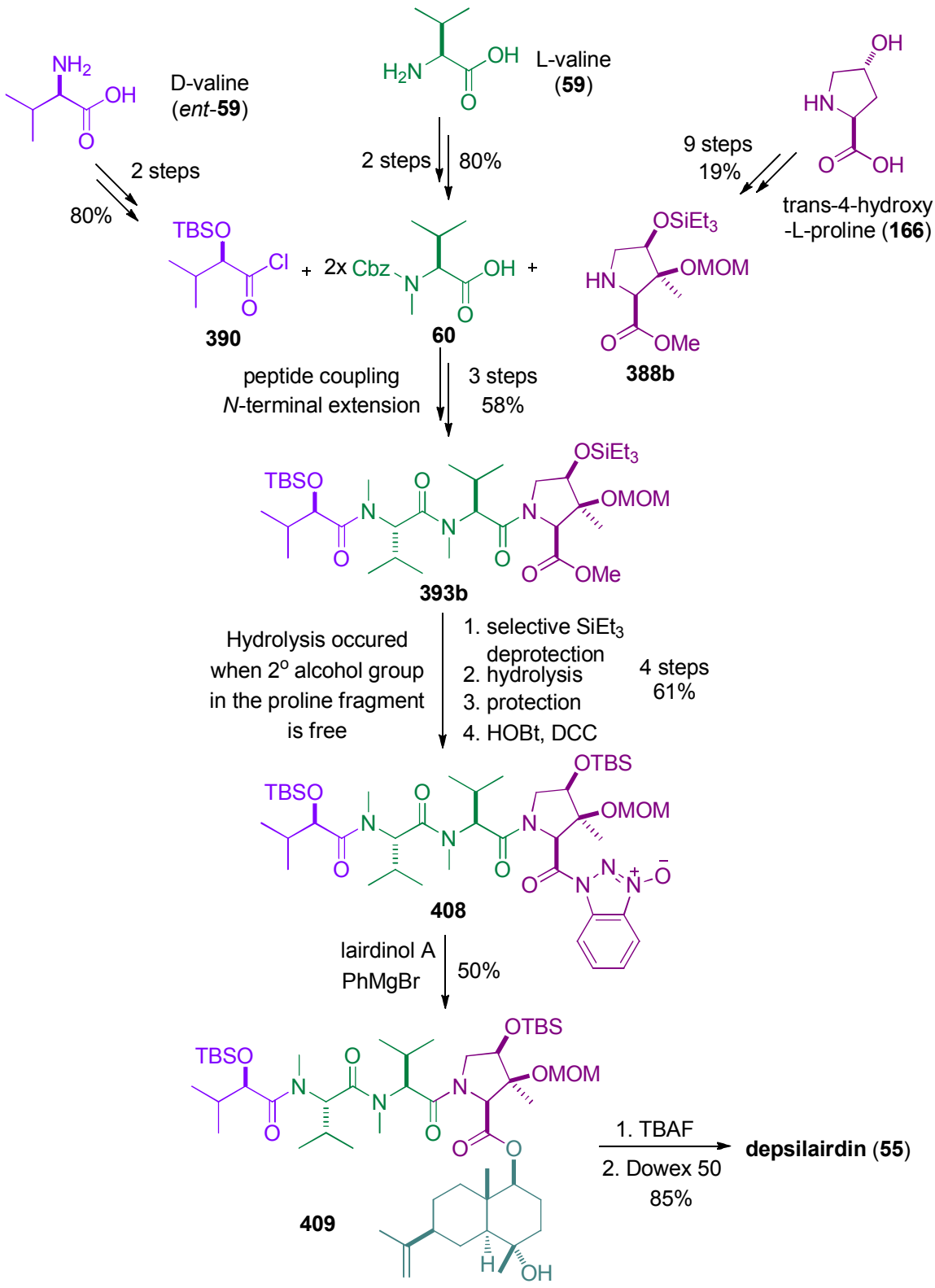

Alkylation of ketone **170** did not proceed as reported by Sardina *et. al*. and was best achieved by optimizing Lubell's protocol using KHMDS as base and 1:1 toluene:DMPU as a solvent to afford the desired product in 55% yield. Thus, the synthes-



-is of fully protected (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline (**388b**) was achieved in 9 steps with 19% overall yield from *trans*-4-hydroxy-L-proline.

The first total synthesis of the host-selective phytotoxin depsilairdin (**55**), which contains a novel sesquiterpene fragment, lairdinol A and a novel (2*S*,3*S*,4*R*)-3,4-dihydroxy-3-methylproline fragment, is achieved in 19 steps with 3% overall yield starting from commercially available *trans*-4-hydroxy-L-proline. The desired tetrapeptide fragment **393** was built up by using the *N*-terminal extension strategy (*C*←*N*) of peptide synthesis. It was noted that the hydrolysis of the tetrapeptide methyl ester did not occur when the proline C-4 hydroxyl was protected as TBS ether. Model studies revealed that the hydrolysis was possible when that hydroxy group in the proline fragment was unprotected. Esterification of the desired tetrapeptide proved very challenging and was ultimately achieved by a new method involving reaction of the HOBt activated tetrapeptide **407** with the bromomagnesium alkoxide of lairdinol A. Deprotection of the resulting depsipeptide **408** furnished depsilairdin (**55**).

Following the same synthetic route, the total syntheses of L-proline, *cis*-4-hydroxy-L-proline and *trans*-4-hydroxy-L-proline analogues of depsilairdin were achieved. Evaluation of the biological activities of depsilairdin and its analogues will be the subject of a future study.


D-valine
(ent-59)
2 steps
80%
L-valine
(59)
2 steps
80%
9 steps
19%
trans-4-hydroxy
-L-proline (166)
390
60
388b
peptide coupling
N-terminal extension
3 steps
58%
393b
Hydrolysis occured
when 2° alcohol group
in the proline fragment
is free
1. selective SiEt3
deprotection
2. hydrolysis
3. protection
4. HOBt, DCC
4 steps
61%
408
lairdinol A
PhMgBr
50%
409
1. TBAF
2. Dowex 50
85%
depsilairdin (55)

# 3 Experimental

## 3.1 General Methods

Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone sodium ketyl; diethyl ether from benzophenone sodium ketyl; $CH_2Cl_2$ from $CaH_2$; toluene from $CaH_2$; MeOH from $Mg(OMe)_2$; $Et_3N$, DIPA, DIPEA, xylene and TMSCl were distilled from $CaH_2$ ($Et_3N$ and DIPEA were stored over KOH). n-BuLi, KHMDS and NaHMDS were routenely titrated[159, 160] using BHT with fluorene as the indicator.[†] Stiker's reagent $[CuH(PPh_3)]_6$ was purchased from Aldrich. $CH_3MgBr$ was titrated using 1M sec-butyl alcohol in dry xylene in the presence of phenanthroline as an indicator.[161] PhMgBr was freshly prepared from bromobenzene using a known procedure by Braun *et al.*[162] and was titrated similar to $CH_3MgBr$.[161] All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with a mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 °C) and $CO_2$(s)/acetone (-78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath.

Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 $F_{254}$. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aq. sulfuric acid (5% v/v), followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still *et al.*[162] with Merck Silica Gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise

[†] BHT (ca. 100 mg, 0.45 mmol) and fluorene (ca. 10 mg) were dissolved in dry THF (2 mL) and cooled to 0 °C under Ar. The organolithium or HMDS was then added dropwise via syringe until a bright yellow end-point persisted.

noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by $^{1}H$ NMR.

### 3.2 Spectral Data

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for $^{1}H$ NMR and 125 MHz for $^{13}C$ NMR. Signals due to the solvent ($^{13}C$ NMR) or residual protonated solvent ($^{1}H$ NMR) served as the internal standard: $CDCl_3$ (7.26 $\delta_H$, 77.23 $\delta_C$); $C_6D_6$ (7.16 $\delta_H$, 128.39 $\delta_C$); $CD_3OD$ (3.31 $\delta_H$, 49.15 $\delta_C$). The $^{1}H$ NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants (*J*) are reported to the nearest 0.5 Hz (digital resolution ca. 0.2 Hz/pt). The $^{1}H$ NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or $^{1}H/^{13}C$ correlation experiments (HSQC and/or HMBC[163] and/or NOE experiments. The $^{13}C$ NMR assignments were made on the basis of chemical shift and multiplicity[†] (as determined by *J*-modulation[164] or HSQC[165]) and were confirmed, where necessary, by two dimensional $^{1}H/^{13}C$ correlation experiments (HSQC and/or HMBC). Specific rotations ($[\alpha]_D$) are the average of 5 determinations at ambient temperature using a 1 mL, 10 dm cell; the units are $10^{-1}$ deg $cm^2$ $g^{-1}$, the concentrations (*c*) are reported in g/100 mL, and the values are rounded to reflect the accuracy of the measured concentrations (the major source of error).

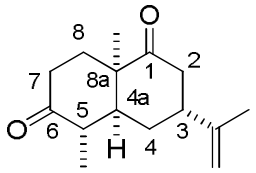
[†] The multiplicity of $^{13}C$ NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = $CH_2$, q = $CH_3$)

## 3.3 Materials

Diene **111b** was prepared from pent-1-en-3-one as reported;[121] the enone precursor is commercially available and was also prepared from 3-pentanone.[166] The Dess-Martin periodinane (DMP) was prepared by an established procedure.[167] The preparation of the following compounds were described previously; Hmb (**56**),[82, 85] *N*-Me-Val (**57**),[12] Cbz-*N*-Me-Val (**60**),[83] *t*-butyldimethylsilyl-(2*R*)-2-(*t*-butyldimethylsilyloxy)-3-methylbutanoate (**389**),[86] MOM-Cl,[168-172] 9-bromo-9-phenyl-9H-fluorene (PfBr) is commercially availaible and was also prepared from fluorenone.[173] Oxodiperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (MoOPH) was prepared using Vedej's procedure.[149] Compound **169** was synthesized in 61% overall yield starting from *trans*-4-hydroxy-L-proline in 4 steps using Sardina's protocol.[61] Dowex 50 is commercially available and was treated (washed sequentially with dist. $H_2O$ (x2), 2N NaOH (x2), 2N HCl (x2), and dist. $H_2O$ till neutral pH).[157] All other reagents were commercially available and unless otherwise noted, were used as received.

## 3.4 Experimental procedures and spectral data

**(3*R*,4a*S*,5*S*,8a*R*)-Hexahydro-5,8a-dimethyl-3-(1-methylethenyl)naphthalene-1,6(2*H*,5*H*)-dione (341a).**




**341a**

**Procedure:** The procedure was adapted from that reported by de Groot *et al.*[54] $EtAlCl_2$ (1 M in hexane; 10 mL, 10 mmol) was added to a stirred solution of (*R*)-(-)-carvone (**104**; 3.0 g, 20 mmol) in dry toluene (70 mL) at room temperature under argon. After 15 min of stirring, the diene **111b** (4.7 g, 30 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and then NaOH (1 M in MeOH; 100 mL, 0.1 mol) was added (note: this step hydrolyzes the TMS enol ethers in the adducts and isomerizes the product from the major Diels-Alder adduct (**338**) (i.e., the 5*R* diastereomer of **341a**) into the thermodynamically more stable title diastereomer). After 24 h, the reaction mixture was neutralized by adding aq. HCl and extracted with $CH_2Cl_2$. The combined organic layers were washed sequentially with saturated aq $NaHCO_3$ and water, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to afford recovered carvone (0.40 g, 13%), a mixture of diastereomers of **341a** (0.72 g, 18%), and the title compound (3.0 g, 64%; 74% based on recovered **104**) as a pale yellow oil.

**$[\alpha]_D$** +30 (*c* 0.3, $CHCl_3$) [lit.[54] for *ent*-**341a**, –36.7 (*c* 0.3, $CHCl_3$)]

**IR** νmax : 3075, 1701, 1638 $cm^{-1}$

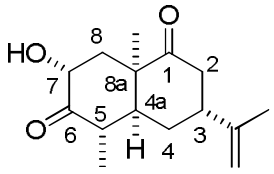
**$^1$H NMR** (500 MHz, $CDCl_3$) δ:[†] 4.83 (1H, br s, HC=C), 4.79 (1H, br s, HC=C), 2.68-2.54 (4H, m, HC-2, HC-3, HC-7, HC-8), 2.43 (1H, br d, *J* = 12 Hz, HC-2), 2.32-2.23 (2H, m, HC-5, HC-7), 2.11-2.04 (1H, m, HC-4), 1.95-1.89 (2H, m, HC-4, HC-4a), 1.79 (3H, s, $H_3CC$=C), 1.43-1.34 (1H, m, HC-8), 1.30 (3H, s, HC-13), 1.02 (3H , d, *J* = 6.5 Hz, HC-12)

**$^{13}$C NMR** (500 MHz, $CDCl_3$) δ: 213.7 (s, C-1), 213.0 (s, C-6), 147.0 (s, C=$CH_2$), 110.4 (t, $CH_2$=C), 52.3 (d, C-4a), 48.9 (s, C-8a), 44.6 (d, C-5), 42.7 (t, C-2), 39.9 (d, C-3), 39.0 (t, C-7), 35.1 (t, C-8), 28.2 (t, C-4), 26.8 (q, $CH_3$C-8a), 20.6 (q, $CH_3$CC-3), 11.5 (q, $CH_3$C-5)

**LRMS** (EI), *m/z* (relative intensity): 234 ([M]$^+$, 100), 219 (6), 179 (11), 137 (29), 123 (31), 109 (96), 93 (35), 67 (57);

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1612, found 234.1618 (EI).

**(3*R*,4a*S*,5*S*,7*R*,8a*R*)-Hexahydro-7-hydroxy-5,8a-dimethyl-3-(1-methylethenyl)naphthalene-1,6(2*H*,5*H*)-dione (345).**




**345**

**Procedure:** A solution of diketone **341a** (2.50 g, 10.7 mmol) and TMSCl (6.80 mL, 5.79 g, 53.3 mmol) in THF (10 mL) was added dropwise via syringe to a stirred solution of LDA [prepared from BuLi (32 mmol) and DIPA (42 mmol)] in dry THF (90 mL) at -78 °C. After 20 min, $Et_3N$ (1.50 mL, 1.07 g, 10.7 mmol) was added. The reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were

[†] These chemical shifts are consistently higher (0.05 for $\delta_H$ and 0.5 for $\delta_C$) than those reported by de Groot for *ent*-**341** (Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1992**, *48*, 3121-3130) presumably due to a different reference assignment.

dried over $Na_2SO_4$ and concentrated to give the bis(TMS enol ether) (4.23 g, 100%). *m*-CPBA (2.33 g, 13.4 mmol) was added to a vigorously stirred solution of the above bis-(TMS enol ether) (4.23 g) in dry $CH_2Cl_2$ (110 mL) at -30 °C under argon. After 1 h, the reaction was quenched by addition of $P(OMe)_3$ (0.66 mL, 0.69 g, 5.6 mmol). The mixture was allowed to warm to ambient temperature and a 9:1 mixture of THF and 10% aq HF (v/v; 100 mL) was added. After 12 h, the mixture was diluted with aq. $K_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to afford the recovered diketone **341a** (0.25 g, 10%), diol **346** (0.20 g, 9%), and the title compound (2.09 g, 78%; 87% based on recovered **341a**) as a thick oil.

**$[\alpha]_D$** +60 (*c* 0.95, $C_6H_6$)

**IR** νmax: 3491, 3074, 1706, 1637 $cm^{-1}$

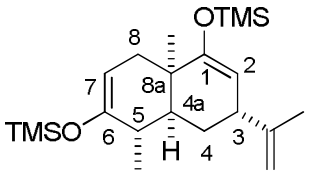
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.85 (1H , br s, HC=C), 4.81 (1H, br s, HC=C), 4.41 (1H, dd, *J* = 7, 12 Hz, HC-7), 3.45 (1H, br s, HO), 2.95 (1H, dd, *J* = 7, 13 Hz, HC-8), 2.67 (1H, dd, *J* = 13, 14 Hz, HC-2), 2.56 (1H, dddd, *J* = 3, 3, 13, 13 Hz, HC-3), 2.44 (1H , dd , *J* = 3, 14 Hz, HC-2), 2.33 (1H, dq, *J* = 11.5, 6.5 Hz, HC-5), 2.10 (1H, ddd, *J* = 3.5, 13, 14 Hz, HC-4), 1.95-1.89 (2H, m, HC-4, HC-4a), 1.79 (3H, s, $H_3$CC-3), 1.33 (3H, s, $H_3$CC-5), 1.19 (1H, dd, *J* = 12, 13 Hz, HC-8), 1.10 (3H, d, *J* = 6.5 Hz, $H_3$CC-5)

**$^{13}$C NMR** (500 MHz, $CDCl_3$) δ: 213.1 (s, C-1), 212.9 (s, C-6), 146.7 (s, C=$CH_2$), 110.6 (t, $CH_2$=C), 71.8 (d, C-7), 52.8 (d, C-4a), 49.2 (s, C-8a), 44.6 (t, C-8), 42.6 (d, C-5), 42.5 (t, C-2), 40.0 (d, C-3), 28.1 (t, C-4), 26.5 (q, $CH_3$C-8a), 20.6 (q, $CH_3$C=C), 11.2 (q, $CH_3$C-5)

**LRMS** (EI), *m/z* (relative intensity): 250 ($[M]^+$, 100), 151 (58), 123 (27), 109 (60), 100 (18), 93 (18), 67 (29)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1568 (EI).

**Bis(TMS enol ether) (343):**

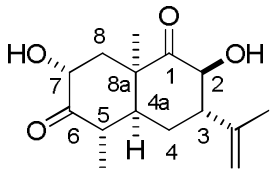



**343**

The crude bis(TMS enol ether) obtained above gave the following spectral properties:

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.77 (1H, brs, $H_2C$=C), 4.74 (1H, brs, $H_2C$=C), 4.68 (1H, dd, *J* = 3, 5 Hz, HC-7), 4.48 (1H, d, *J* = 3.5 Hz, HC-2), 2.95 (1H, ddd, *J* = 3.5, 6.5, 8.5 Hz, HC-3), 2.35 (1H, dd, *J* = 5, 16 Hz, HC-8), 2.00 (1H, dq, *J* = 6, 7 Hz, HC-5), 1.78 (1H, ddd, *J* = 3, 3, 16,5 Hz, HC-8), 1.75 (3H, s, $H_3CC$=C), 1.73 (1H, dd, *J* = 6, 6.5, 13 Hz, HC-4), 1.63 (1H, dddd, *J* = 3.5, 8.5, 13 Hz, HC-4), 1.51 (1H, ddd, *J* = 3.5, 6, 6 Hz, HC-4a), 1.30 (3H, s, $H_3CC$-8a), 1.11 (3H, d, *J* = 7 Hz, $H_3CC$-5), 0.19 (9H, s, $(H_3C)_3Si$), 0.17 (9H, s, $(H_3C)_3Si$).

**(2*S*,3*S*,4a*S*,5*S*,7*R*,8a*R*)-Hexahydro-2,7-dihydroxy-5,8adimethyl-3-(1-methylethenyl)-naphthlene-1,6(2*H*,5*H*)-dione (346)**




**346**

**[α]$_D$** -5 (*c* 0.5, $CH_2Cl_2$)

**IR νmax**: 3467, 3070, 1718, 1664 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.95 (1H, br s, HC=C), 4.91 (1H, br s, HC=C), 4.47 (1H, d, *J* = 11.5 Hz, HC-2), 4.43 (1H, dd, *J* = 7.5, 12 Hz, HC-7), 3.62 (1H, br s, HO), 3.42 (1H, br s, HO), 2.90 (1H, dd, *J* = 7.5, 13.5 Hz, HC-8), 2.38 (1H, ddd, *J* = 3.5, 11.5, 13.5

Hz, HC-3), 2.19-2.26 (1H, dq, *J* = 12.5, 6.5 Hz, HC-5), 2.14 (1H, ddd, *J* = 4, 13.5, 15.5 Hz, HC-4), 1.84 (1H, ddd, *J* = 2.5, 4, 12.5 Hz, HC-4a), 1.79 (3H, br s, $H_3CC$=C), 1.74 (1H, ddd, *J* = 2.5, 3.5, 15.5 Hz, HC-4), 1.31 (3H, s, $H_3CC$-8a), 1.19 (1H, dd, *J* = 12, 13.5 Hz, HC-8), 1.00 (3H, d, *J* = 6.5 Hz, $H_3CC$-5)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 213.4 (s, C-1 or C-6), 212.4 (s, C-1 or C-6), 144.2 (s, C=$CH_2$), 113.3 (t, $CH_2$=C), 73.6 (d, C-2), 71.6 (d, C-7), 53.0 (d, C-4a), 49.6 (d, C-3), 48.8 (s, C-8a), 44.9 (t, C-8), 42.3 (s, C-5), 27.3 (t, C-4), 26.7 (q, $CH_3$C-8a), 19.7 (q, $CH_3$C=C), 11.2 (q, $CH_3$C-5)

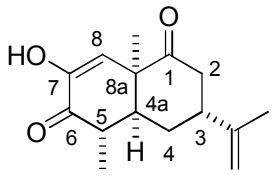
**LRMS** (EI), *m/z* (relative intensity): 266 ($[M]^+$, 100), 248 (6), 197 (8), 167 (31), 152 (14), 139 (15), 85 (38), 69 (27)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1513 (EI).

**(3*R*,4a*S*,5*S*,8a*R*)-3,4,4a,8a-Tetrahydro-7-hydroxy-5,8adimethyl-3-(1-methylethenyl)-1,6(2*H*, 5*H*)-naphthalenedione (347)**

**Procedure:** Dry DMSO (1.4 mL, 1.6 g, 20 mmol) was added dropwise via syringe to a solution of oxalyl chloride (0.87 mL, 1.3 g, 10 mmol) in dry $CH_2Cl_2$ (80 mL) at -78 °C under argon. After 30 min, a solution of ketol **345** (2.09 g, 8.35 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise via syringe. After 1 h, DIPEA (4.4 mL, 3.2 g, 25 mmol) was added and the reaction mixture was allowed to warm to ambient temperature over 30 min. The mixture was diluted with $CH_2Cl_2$, washed sequentially with 10% aq HCl and saturated $NaHCO_3$, and concentrated to afford the crude 1,2-diketone (2.2 g) that was primarily in the undesired enol form 10a (ca. 10:1). The crude mixture of enols was applied onto a silica gel column [prepared from a slurry of silica gel (50 g) in 5% (v/v) $Et_3N$ in hexane] and eluted with 20% ethyl acetate in hexane to obtain the title compound as a white sticky solid (1.99 g, 95%):

Spectroscopic data for a 10:1 mixture of **347** and **348**, respectively




**347**

**[α]$_D$** -99, (*c* 1.62, $C_6H_6$)

**IR** νmax: 3418, 3077, 1702, 1678 $cm^{-1}$

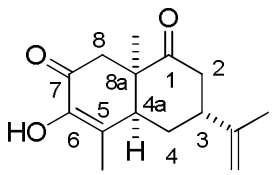
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 6.01 (1H, s, HO), 5.99 (1H, s, HC-8), 4.84 (1H, br s, HC=C), 4.80 (1H, br s, HC=C), 2.68 (1H, dd, *J* = 12.5, 13.5 Hz, HC-2), 2.50 (1H, dddd, *J* = 3.5, 4, 12.5, 13 Hz, HC-3), 2.41 (1H, ddd, *J* = 2, 4, 13.5 Hz, HC-2), 2.39 (1H, dq, *J* = 7, 13 Hz, HC-5), 2.21 (1H, ddd, *J* = 3, 4, 13 Hz, HC-4a), 2.11 (1H, ddd, *J* = 4, 13, 14.5 Hz, HC-4), 1.95 (1H, dddd, *J* = 2, 3, 3.5, 14.5 Hz, HC-4), 1.79 (3H, s, $H_3CC$=C), 1.51 (3H, s, $H_3CC$-8a), 1.18 (3H, d, *J* = 7 Hz, $H_3CC$-5)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 213.2 (s, C-1), 196.8 (s, C-6), 146.6 (s, C=$CH_2$), 145.0 (s, C-7), 121.6 (d, C-8), 110.6 (t, $CH_2$=C), 50.8 (s, C-8a), 48.9 (d, C-4a), 42.8 (t, C-2), 40.6 (d, C-5), 40.3 (d, C-3), 27.9 (t, C-4), 26.4 (q, $CH_3C$-8a), 20.7 (q, $CH_3C$=C), 11.3 (q, $CH_3C$-5)

**LRMS** (EI), *m/z* (relative intensity): 248 ($[M]^+$, 12), 205 (7), 151 (23), 138 (100), 123 (13), 110 (75), 95 (25), 67 (14)

**HRMS** *m/z* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1409 (EI).

**(3*R*,4a*S*,8a*R*)-3,4,4a,8a-Tetrahydro-6-hydroxy-5,8adimethyl-3-(1-methylethenyl)-1,7(2*H*, 8*H*)-naphthalenedione (348).**




**348**

**[α]$_D$** +78 (*c* 2.0, $CH_2Cl_2$)

**IR** νmax: 3411, 3075, 1705, 1670, 1648 $cm^{-1}$

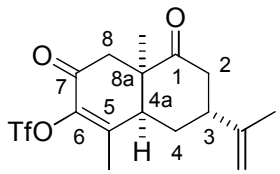
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 6.12 (1H, br s, HO), 4.88 (1H, brs, HC=C), 4.79 (1H, brs, HC=C), 3.05 (1H, d, *J* = 16.5 Hz, HC-8), 2.85 (1H, br s, HC-4a), 2.59 (1H , br dd, *J* = 13.5, 14 Hz, HC-2), 2.47-2.38 (2H, m, HC-2, HC-3), 2.23-2.10 (3H, m, $H_2C$-4, HC-8), 1.89 (3H, s, $H_3CC$-5), 1.81 (3H, s, $H_3CCC$-3), 1.36 (3H, s, $H_3CC$-8a)

**$^{13}$C NMR** (500 MHz, $CDCl_3$) δ: 211.4 (s, C-1), 191.5 (s, C-7), 146.9 (s, $C=CH_2$), 145.5 (s, C-6), 126.9 (s, C-5), 110.9 (t, $CH_2$=C), 49.7 (s, C-8a), 47.1 (d, C-4a), 43.5 (t, C-8), 42.5 (t, C-2), 41.3 (d, C-3), 29.3 (t, C-4), 24.4 (q, $CH_3$C-8a), 20.8 (q, $CH_3C$=C), 13.9 (q, $CH_3$C-5)

**LRMS** (EI), *m/z* (relative intensity): 248 ($[M]^+$, 90), 205 (82), 151 (78), 138 (100), 110 (72), 95 (52), 67 (47);

**HRMS** *m/z* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1411.

**(3*R*,4a*S*,8a*R*)-1,2,3,4,4a,7,8,8a-Octahydro-5,8a-dimethyl-1,7-dioxo-3-(1-methyleth-enyl)naphthalen-6-yltrifluoromethanesulfonate (349).**




**349**

**Procedure:** DIPEA (2.50 mL, 1.86 g, 14.4 mmol) and $Tf_2O$ (1.75 mL, 2.93 g, 10.4 mmol) were added sequentially to a stirred solution of disophenol **348** (1.99 g, 8.01 mmol) in dry $CH_2Cl_2$ (80 mL) at 0 °C under argon. After 10 min, the reaction mixture was diluted with ethyl acetate, washed sequentially with 10% aq. HCl, saturated $NaHCO_3$, and brine, dried over $Na_2SO_4$, and concentrated to give the triflate (**349**) (3.07 g, 100%) as a yellow-brown solid that was essentially homogeneous by $^1$H NMR.

**[α]$_D$** –7 (*c* 1.1, $C_6H_6$)

**IR** νmax: 3074, 1711, 1635, 1420, 1204, 1128 cm$^{-1}$

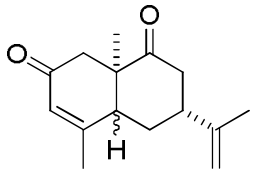
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.89 (1H, br s, HC=C), 4.75 (1H, br s, HC=C), 3.03 (1H, d, *J* = 16.5 Hz, HC-8), 2.92 (1H, dd, *J* = 4, 5.5 Hz, HC-4a), 2.64 (1H, dd, *J* = 10, 15 Hz, HC-2), 2.53 (1H, dd, *J* = 4.5, 15 Hz, HC-2), 2.43 (1H, dddd, *J* = 4, 4.5, 9.5, 10 Hz, HC-3), 2.27 (1H, ddd, *J* = 4, 9.5 14.5 Hz, HC-4), 2.26 (1H, d, *J* = 16.5 Hz, HC-8), 2.16 (1H, ddd, *J* = 4, 5.5, 14.5 Hz, HC-4), 2.04 (3H, s, $H_3CC$-5), 1.78 (3H, s, $H_3CC$-3), 1.36 (3H, s, $H_3CC$-8a)

**$^{13}$C NMR** (500 MHz, $CDCl_3$) δ: 210.2 (s, C-1), 186.4 (s, C-7), 150.2 (s, C-6), 145.8 (s, $C{=}CH_2$), 142.7 (s, C-5), 118.7 (s, $CF_3$ [$J_{CF}$, 320 Hz]), 112.1 (t, $CH_2{=}C$), 48.9 (s, C-8a), 48.0 (d, C-4a), 44.4 (t, C-8), 41.9 (t, C-2), 41.0 (d, C-3), 28.9 (t, C-4), 23.4 (q, $CH_3C$-8a), 21.0 (q, $CH_3CC$-3), 16.6 (q, $CH_3C$-5)

**LRMS** (EI), *m/z* (relative intensity): 380 ([M]$^+$, 25), 270 (10), 247 (22), 151 (18), 137 (36), 109 (100), 81 (37), 67 (38)

**HRMS** *m/z* calcd for $C_16H_{19}F_3O_5S$ 380.0905, found 380.0910 (EI).

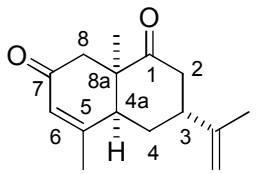
**(3*R*,4a*RS*,8a*R*)-3,4,4a,8a-Hexahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,7(2*H*,8*H*)-naphthalenedione (350).**



**350**

**Procedure:** The crude triflate (**349**) (3.07 g, ca. 8.07 mmol) and $Et_3SiH$ (3.90 mL, 2.81 g, 24.2 mmol) were added sequentially to a stirred solution of $Pd(PPh_3)_4$ (0.47 g, 0.40 mmol) and LiCl (0.167 g, 24.2 mmol) in dry DMF (81 mL) at room temperature under argon. The reaction mixture was heated to 60 °C for 2 h after which time the mixture had turned black indicating the reaction was complete. The mixture was allowed to cool to ambient temperature and then was diluted with ethyl acetate (300 mL), washed sequentially with water and brine, dried over $Na_2SO_4$, and concentrated. The residue was taken up in $CH_2Cl_2$ and passed through a short pad of silica gel eluting with 25% ethyl acetate in hexane to afford a 13:1 mixture of **350a** and **350b**, respectively (1.90 g, ca. 95% pure by $^1$H NMR). The crude products from similar reactions (10-13:1 mixtures of **350a** and **350b**, respectively) could be fractionated by FCC (25% ethyl acetate in hexane) to afford **350a** (80-85%) and **350b** (5-8%) as white solids.

**(3*R*,4a*S*,8a*R*)-3,4,4a,8a-Hexahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,7(2*H*,8*H*)-naphthalenedione (350a)**




**350a**

**$[\alpha]_D$** –44 (*c* 0.83, $C_6H_6$)

**IR** νmax: 3075, 1705, 1661 $cm^{-1}$

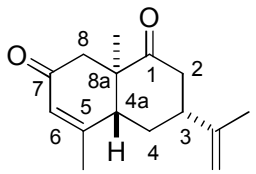
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.94 (1H , br s, HC-6), 4.89 (1H , br s, $H_2C$=C), 4.75 (1H, br s, $H_2C$=C), 2.84 (1H, d, *J* = 16 Hz, HC-8), 2.64 (1H, dd, *J* = 4, 5.5 Hz, HC-4a), 2.63 (1H, dd, *J* = 9.5, 15 Hz, HC-2), 2.52 (1H, dd, *J* = 5, 15 Hz, HC-2), 2.45 (1H, dddd, *J* = 4.5, 5, 9, 9.5 Hz, HC-3), 2.20 (1H, ddd, *J* = 4, 9, 14.5 Hz, HC-4), 2.09 (1H, ddd, *J* = 4.5, 5.5, 14.5 Hz, HC-4), 2.08 (1H, d, *J* = 16 Hz, HC-8), 1.96 (3H, s, $H_3$CC-5), 1.79 (3H, s, $H_3$CC-3), 1.31 (3H, s, $H_3$CC-8a)

**$^{13}$C NMR** (500 MHz, $CDCl_3$) δ: 211.8 (s, C-1), 196.4 (s, C-7), 160.2 (s, C-5), 146.3 (s, C=$CH_2$), 128.8 (d, C-6), 111.8 (t, $CH_2$=C), 50.1 (s, C-8a), 46.8 (d, C-4a), 44.6 (t, C-8), 42.1 (t, C-2), 41.1 (d, C-3), 28.7 (t, C-4), 23.7 (q, $CH_3$C-8a), 22.6 (q, $CH_3$C-5), 21.2 (q, $CH_3$CC-3);

**LRMS** (EI), *m/z* (relative intensity): 232 ($[M]^+$, 51), 167 (8), 149 (20), 109 (38), 123 (100), 110 (26), 93 (2), 79 (30)

**HRMS** *m/z* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1464 (EI).

**(3*R*,4a*R*,8a*R*)-3,4,4a,8a-Hexahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,7(2*H*,8*H*)-naphthalenedione (350b)**




**350b**

**[α]$_D$** +62 (*c* 0.91, $C_6H_6$)

**IR** νmax: 3079, 2972, 1708, 1673, 1627 $cm^{-1}$

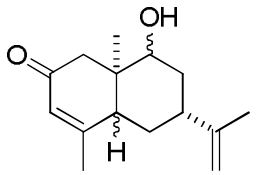
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.92 (1H, br s, HC-6), 4.85 (1H, br s, $H_2C$=C), 4.83 (1H, br s, $H_2C$=C), 2.69 (1H, br d, *J* = 13 Hz, HC-4a), 2.66 (1H, dd, *J* = 13, 14 Hz, HC-2), 2.58 (1H, d, *J* = 17 Hz, HC-8), 2.51 (1H, br d, *J* = 17 Hz, HC-8), 2.44 (1H, dddd, *J* = 3.5, 4.5, 13, 13 Hz, HC-3), 2.38 (1H, ddd, *J* = 1.5, 4.5, 14 Hz, HC-2), 2.16 (1H, dddd, *J* = 1.5, 3.5, 4, 13 Hz, HC-4), 1.99 (3H, dd, *J* = 1.5, 1.5 Hz, $H_3$CC-5), 1.80 (3H, br s, $H_3$CC=C), 1.77 (1H, ddd, *J* = 13, 13, 13 Hz, HC-4), 1.16 (3H, s, $H_3$CC-8a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 211.7 (s, C-1), 198.0 (s, C-7), 159.3 (s, C-5), 146.8 (s, C=$CH_2$), 127.5 (d, C-6), 110.9 (t, $CH_2$=C), 50.7 (s, C-8a), 47.2 (d, C-4a), 46.5 (t, C-8), 45.3 (d, C-3), 41.5 (t, C-2), 28.1 (t, C-4), 22.4 (q, $CH_3$C-5), 20.5 (q, $CH_3$C=C), 17.3 (q, $CH_3$C-8a)

**LRMS** (EI), *m/z* (relative intensity): 232 ($[M]^+$, 76), 189 (13), 137 (63), 107 (75), 93 (100), 79 (58), 69 (93), 53 (33)

**HRMS** *m/z* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1466 (EI).

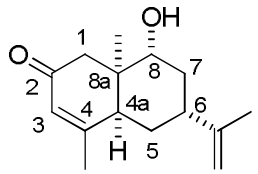
**(4a*RS*,6*R*,8*RS*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-8-hydroxy-4,8a-dimethyl-6-(1-methyl-ethenyl)naphthalen-2(1*H*)-one (351).**




**351**

**Procedure:** $NaBH_4$ (1.82 g, 48.0 mmol) was added to a stirred solution of the above 13:1 mixture of crude diketones **350a** and **350b** (1.90 g) in a 1:1 (v/v) mixture of $CH_2Cl_2$ and MeOH (2.5 mL) at -78 °C under argon. After 16 h, the reaction was quenched by dropwise addition of acetone (10 mL). The mixture was allowed to warm to ambient temperature and then was diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, and concentrated to give the crude product (2.3 g) that was a 72:14:6:8 mixture (by 1H NMR) of **351b**, **351a**, **351c**, and **350a**, respectively (1.82 g). Fractionation of the crude by FCC (20% ethyl acetate in hexane) afforded recovered **350a** (0.17 g, 9%) and a 12:2:1 mixture (by 1H NMR) of **351b**, **351a**, and **351c**, respectively (1.50 g, 80% from diosphenol **348**). Under the same reaction conditions, reduction of cis **350a** gave a separable 5.5:1 mixture (by 1H NMR of the crude product) of **351b** (80%) and **351a** (10%) after fractionation of the crude by FCC (25% ethyl acetate in hexane). Similarly, reduction of trans **350b** gave a separable 25:1 mixture (by 1H NMR of the crude product) of **351c** (84%) as a white solid and **351d** (not isolated but obtained by isomerization of **351b**) after fractionation of the crude by FCC (25% ethyl acetate in hexane). In these cases as well as in smaller scale reductions of the **350a/350b** mixture, **350** was completely consumed.

**(4aS,6R,8R,8aR)-4a,5,6,7,8,8a-Hexahydro-8-hydroxy-4,8adimethyl-6-(1-methylethenyl)naphthalen-2(1*H*)-one (351a)**




**351a**

**[α]$_D$** +25 (*c* 0.43, $C_6H_6$)

**IR** νmax: 3423, 3079, 1658, 1640 $cm^{-1}$

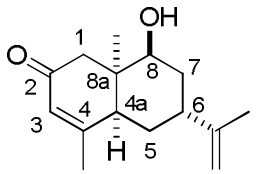
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.97 (1H, br s, HC-3), 4.76 (1H, br s, $H_2C$=C), 4.75 (1H, br s, $H_2C$=C), 3.78 (1H, ddd, *J* = 5, 5, 11 Hz, HC-8), 2.81 (1H, d, *J* = 16 Hz, HC-1), 2.60 (1H, dd, *J* = 5, 5 Hz, HC-4a), 2.22 (1H, d, *J* = 16 Hz, HC-1), 2.00-1.93 (1H, m, HC-5), 1.94 (3H, s, $H_3$CC-4), 1.91-1.71 (3H, m, HC-5, HC-6, HC-7), 1.85 (1H, d, *J* = 5 Hz, HO), 1.76 (3H, s, $H_3$CC=C), 1.52 (1H, ap ddd, *J* = 11, 12, 12 Hz, HC-7), 1.14 (3H, s, $H_3$CC-8a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 199.2 (s, C-2), 161.9 (s, C-4), 148.4 (s, C=$CH_2$), 129.0 (d, C-3), 109.6 (t, $CH_2$=C), 69.6 (d, C-8), 48.0 (t, C-1), 47.1 (d, C-4a), 41.3 (s, C-8a), 40.3 (d, C-6), 35.6 (t, C-7), 28.1 (t,C-5), 22.5 (q, $CH_3$C-4), 20.9 (q, $CH_3$C=C), 20.4 (q, $CH_3$C-8a)

**LRMS** (EI), *m/z* (relative intensity): 234 ($[M]^+$,45), 219 (12), 191 (17), 176 (35), 137 (75), 123 (100), 109 (36), 79 (35)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1623 (EI).

**(4a*S*,6*R*,8*S*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-8-hydroxy-4,8adimethyl-6-(1-methyleth-enyl)naphthalen-2(1H)-one (351b)**




**351b**

**[α]$_D$** –23 (*c* 1.6, $C_6H_6$)

**IR** νmax: 3439, 3075, 1661 $cm^{-1}$

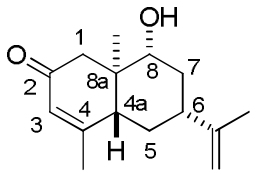
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.85 (1H, br s, HC-3), 4.93 (1H, br s, $H_2C$=C), 4.84 (1H, br s, $H_2C$=C), 3.61 (1H, br d, *J* = 9 Hz, HC-8), 2.52 (1H, d, *J* = 17 Hz, HC-1), 2.45 (1H, br s, HC-6), 2.20 (1H, d, *J* = 17 Hz, HC-1), 2.17-1.98 (4H, m, HO, HC-4a, HC-5, HC-7), 1.96 (3H, s, $H_3$CC-4), 1.78 (3H, s, $H_3$CC=C), 1.74 (1H, ddd, *J* = 5, 11, 13 Hz, HC-7), 1.64-1.57 (1H, m, HC-5), 1.09 (3H, s, $H_3$C-8a)

**$^{13}$C NMR** (500 MHz, $CDCl_3$) δ: 199.6 (s, C-2), 163.5 (s, C-4), 146.2 (s, C=$CH_2$), 126.5 (d, C-3), 111.1 (t, $CH_2$=C), 73.3 (br, C-8), 44.5 (d, C-4a), 41.0, 37.5 (br), 32.9 (br t, C-7), 29.9 (t, C-5), 24.9 (br q, $CH_3$C-8a), 23.4 (q, $CH_3$C-4), 22.4 (q, $CH_3$C=C), [note:several signals are broad (br) and one carbon is 'missing' due to slow conformational exchange]

**LRMS** (EI), *m/z* (relative intensity): 234 ($[M]^+$, 25), 191 (11), 173 (5), 137 (37), 123 (100), 109 (23), 94 (11), 79 (20)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1621 (EI).

**(4a*R*,6*R*,8*R*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-8-hydroxy-4,8adimethyl-6-(1-methyleth-enyl)naphthalen-2(1*H*)-one (351c)**




**351c**

**[α]$_D$** –82 (*c* 1.3, $C_6H_6$)

**IR** νmax: 3432, 3073, 1656, 1619 $cm^{-1}$

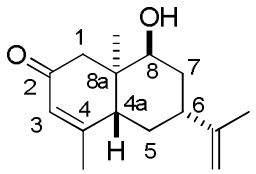
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.91 (1H, br s, HC-3), 4.79 (2H, br s, $H_2C$=C), 3.59 (1H, ddd, *J* = 5.5, 5.5, 13 Hz, HC-8), 2.75 (1H, d, *J* = 16 Hz, HC-1), 2.39 (1H, br d, *J* = 13 Hz, HC-4a), 2.22-2.12 (1H, m, HC-6), 2.16 (1H, d, *J* = 16 Hz, HC-1), 1.94 (3H, s, $H_3$CC-4), 1.93 (1H, dddd, *J* = 1, 3, 3, 13 Hz, HC-5), 1.86 (1H, dddd, *J* = 1, 5.5, 5.5, 13 Hz, HC-7), 1.78 (3H, s, $H_3$CC=C), 1.54 (1H,ddd, *J* = 13, 13, 13 Hz, HC-7), 1.45 (1H, d, *J* = 5.5 Hz, HO), 1.34 (1H, ddd, *J* = 13, 13, 13 Hz, HC-5), 0.90 (3H, s, $H_3$CC-8a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 198.6 (s, C-2), 161.8 (s, C-4), 148.4 (s, C=$CH_2$), 127.1 (d, C-3), 109.9 (t, $CH_2$=C), 77.64 (d, C-8), 50.5 (t, C-1), 48.5 (d, C-4a), 43.4 (d, C-6), 42.9 (s, C-8a), 34.9 (t, C-7), 28.1 (t, C-5), 22.6 (q, $CH_3$C-4), 20.9 (q, $CH_3$C=C), 11.2 (q, $CH_3$C-8a)

**LRMS** (EI), *m/z* (relative intensity): 234 ($[M]^+$,66), 219 (6), 201 (9), 175 (11), 137 (73), 123 (40), 95 (100), 79 (70)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1623 (EI).

**(4a*R*,6*R*,8*S*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-8-hydroxy-4,8adimethyl-6-(1-methyleth-enyl)naphthalen-2(1*H*)-one (351d).**




**351d**

**Procedure:** A solution of cis alcohol **351b** (20 mg, 0.085 mmole) in degassed methanolic NaOH (0.4 M; 0.85 ml) stirred at ambient temperature under argon. After 17 h, the reaction was neutralized (pH ca. 7) by addtition of aq. HCl and extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, concentrated, and fractionated by PTLC (ether) to give **351b** (7 mg, 35%) and **351d** (0.012 g, 60%) as an oil.

**$[\alpha]_D$** –40 (*c* 0.6, $C_6H_6$)

**IR** νmax: 3439, 3079, 1653 $cm^{-1}$

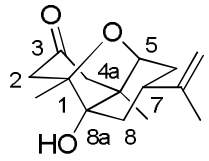
**$^1$H NMR** (500 MHz, $CD_3OD$) δ: 5.84 (1H, s, HC-3), 4.79 (1H, br s, $H_2C$=C), 4.76 (1H, br s, $H_2C$=C), 3.52 (1H, dd, *J* = 3, 3 Hz, HC-8), 2.98 (1H, dd, *J* = 3, 13 Hz, HC-4a), 2.86 (1H, d, *J* = 16 Hz, HC-1), 2.56 (1H, dddd, *J* = 3, 3, 13, 13 Hz, HC-6), 1.93-2.02 (2H, m, HC-1, HC-5), 1.97 (3H, s, $H_3$CC-4), 1.81 (1H, ddd, *J* = 3, 13, 13 Hz, HC-7), 1.78 (3H, s, $H_3$CC=C), 1.71 (1H, ddd, *J* = 3, 3, 13 Hz, HC-7), 1.39 (1H, ddd, *J* = 13, 13, 13 Hz, HC-5), 0.89 (3H, s, $H_3$CC-8a)

**$^{13}$C NMR** (125 MHz, $CD_3OD$) δ: 203.3 (s, C-2), 167.6 (s, C-4), 151.0 (s, C=$CH_2$), 126.7 (d, C-3), 109.8 (t, $CH_2$=C), 74.6 (d, C-8), 50.1 (t, C-1), 43.7 (s, C-8a), 42.4 (d, C-4a), 40.7 (d, C-6), 34.2 (t, C-7), 29.6 (t, C-5), 22.4 (q, $CH_3$C-4), 21.1 (q, $CH_3$C=C), 17.7 (q, $CH_3$C-8a)

**LRMS** (EI), *m/z* (relative intensity): 234 ([M]$^+$, 11), 216 (7), 173 (5), 145 (5), 129 (66), 114 (96), 95 (8), 72 (100)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1619 (EI).

**(1*S*,4a*S*,5*S*,7*S*,8a*S*)-Octahydro-8a-hydroxy-1,4a-dimethyl-7-(1-methylethenyl)-1,5-epoxynapthalen-3(2*H*)-one (357).**




**357**

**Procedure:** A solution of **351b** (10 mg, 0.043 mmol) in methanolic NaOH (0.4 M, 0.5 mL, 0.2 mmol) was stirred at room temperature under air for 3 days. The reaction was neutralized by addition of aq. HCl and then extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, concentrated, and fractionated by PTLC (30 % ethyl acetate in hexane) to afford the epoxide **355b** (3 mg, 27%) (spectroscopic data listed below) and the title compound (5 mg, 45%) as a white solid.

**[α]$_D$** –10 (*c* 0.26, $C_6H_6$)

**IR** νmax: 3377, 3075, 1712, 1644 cm$^{-1}$

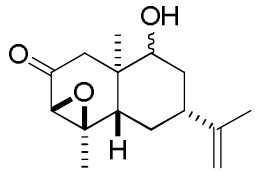
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.80 (1H, br s, $H_2C$=C), 4.78 (1H, br s, $H_2C$=C), 4.04 (1H, d, *J* = 4.5 Hz, HC-5), 2.90 (1H, d, *J* = 16.5 Hz, HC-2), 2.76 (1H, dddd, *J* = 7.5, 7.5, 11.5, 11.5 Hz, HC-7), 2.69 (1H, d, *J* = 17 Hz, HC-4), 2.35 (1H, dd, *J* = 2.5, 16.5 Hz, HC-2), 2.23 (1H, dd, *J* = 2.5, 17 Hz, HC-4), 1.92 (1H, dd, *J* = 11.5, 13.5 Hz, HC-8), 1.89 (1H, dd, *J* = 7.5, 13.5 Hz, HC-8), 1.83 (1H, ddd, *J* = 4.5, 7.5, 14 Hz, HC-7), 1.79 (3H, s, $H_3$CC=C), 1.55 (1H, dd, *J* = 11.5, 14 Hz, HC-6), 1.33 (3H, s, $H_3$CC-1), 1.02 (3H, s, $H_3$CC-4a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 209.5 (s, C-3), 147.5 (s, $C{=}CH_2$), 109.8 (t, $CH_2{=}C$), 83.1 (d, C-5), 82.2 (s, C-1), 76.8 (s, C-8a), 51.7 (t, C-2), 50.2 (t, C-4), 46.4 (s, C-4a), 37.2 (d, C-7), 35.1 (t, C-8), 31.6 (t, C-6), 21.0 (q, $CH_3C{=}C$), 19.5 (q, $CH_3C$-1), 17.1 (q, $CH_3C$-4a)

**LRMS** (EI), *m/z* (relative intensity): 250 ($[M]^+$, 32), 232 (24), 189 (11), 164 (36), 151 (100), 128 (16), 109 (76), 69 (30)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1564 (EI).

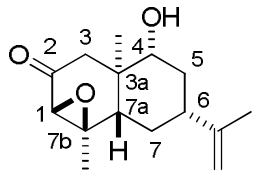
**(1a*R*,3a*R*,4*RS*,6*R*,7a*S*,7b*R*)-Octahydro-4-hydroxy-3a,7bdimethyl-6-(1-methyleth-enyl)naphth[1,2-b]oxiren-2(1a*H*)-one (355).**




**355**

**Procedure:** An aqueous solution of $H_2O_2$ (30% in $H_2O$; 2.6 mL, 26 mmol) was added dropwise over 5 min to a solution of the above crude mixture of alcohols **351** (1.50 g, 6.40 mmol) in methanolic NaOH (0.4 M, 128 mL, 0.05 mol) at room temperature. After 24 h, the reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, concentrated, and passed through a short pad of silica gel eluting with 25% ethyl acetate in hexane to obtain a 4:1 mixture of alcohols **355b** and **355a**, respectively (1.21 g, 75%). Under the same reaction conditions, oxidation of **351b** gave **355b** (78%) after fractionation of the crude by FCC (20% ethyl acetate in hexane). Similarly, oxidations of **351a** or **351c** gave **355a** in 78-80% yields after fractionation of the crude products by FCC (20% ethyl acetate in hexane) as white solids.

**(1a*R*,3a*R*,4*R*,6*R*,7a*S*,7b*R*)-Octahydro-4-hydroxy-3a,7bdimethyl-6-(1-methylethenyl)naphtho[2,1-b]oxiren-2(1a*H*)-one (355a)**




**355a**

**[α]$_D$** –42 (*c* 1.1, $C_6H_6$)

**IR** νmax: 3469, 3079, 1715, 1645 $cm^{-1}$

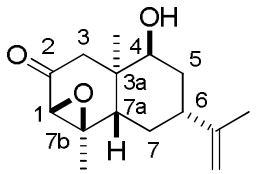
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.78 (1H, br s, HC=C), 4.76 (1H, br s, HC=C), 3.45 (1H, dd, *J* = 4.5, 13 Hz, HC-4), 3.02 (1H, s, HC-1a), 2.51 (1H, d, *J* = 14 Hz, HC-3), 2.32 (1H, d, *J* = 14 Hz, HC-3), 2.11 (1H, dddd, *J* = 4, 4, 13, 13 Hz, HC-6), 2.03 (1H, dd, *J* = 3, 13 Hz, HC-7a), 1.90-1.80 (2H, m, HC-5 & 7), 1.77 (3H, s, $CH_3C$=C), 1.47 (1H, ddd, *J* = 13, 13, 13 Hz, HC-5), 1.37 (3H, s, $CH_3C$-7b), 1.31 (1H, ddd, *J* = 13, 13, 13 Hz, HC-7), 0.83 (3H, s, $CH_3C$-3a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 206.7 (s, C-2), 148.2 (s, C=$CH_2$), 110.0 (t, $CH_2$=C), 76.1 (d, C-4), 65.6 (s, C-7b), 62.8 (d, C-1a), 47.4 (t, C-3), 46.8 (d, C-7a), 45.1 (s, C-3a), 43.2 (d, C-6), 35.2 (t, C-5), 28.7 (t, C-7), 21.0 (q, $CH_3C$=C or $CH_3C$-7a), 20.9 (q, $CH_3C$-7a or $CH_3C$=C), 12.4 (q, $CH_3C$-3a)

**LRMS** (EI), *m/z* (relative intensity): 250 ($[M]^+$, 2), 235 (8), 207 (6), 189 (9), 153 (100), 123 (12), 107 (28)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1565 (EI).

**(1a*R*,3a*R*,4*S*,6*R*,7a*S*,7b*R*)-Octahydro-4-hydroxy-3a,7bdimethyl-6-(1-methyleth-enyl)naphth[1,2-b]oxiren-2(1a*H*)- one (355b)**




**355b**

**[α]$_D$** –18 (c 2.3, $C_6H_6$)

**IR** νmax: 3491, 3080, 1706,1638 $cm^{-1}$

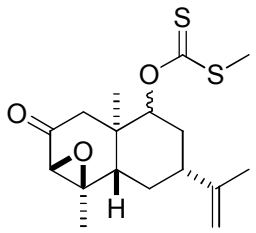
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.79 (1H, br s, HC=C), 4.78 (1H, br s, HC=C), 3.51 (1H, br s, HC-4), 3.01 (1H, s, HC-1a), 2.99 (1H, d, *J* = 14 Hz, HC-3), 2.63 (1H, dd, *J* = 3, 13.5 Hz, HC-7a), 2.48 (1H, dddd, *J* = 3, 4, 12.5, 13 Hz, HC-6), 1.91 (1H, ddd, *J* = 4, 4, 13 Hz, HC-7), 1.84 (1H, d, *J* = 14 Hz, HC-3), 1.80 (1H, ddd, *J* = 3, 13, 13 Hz, HC-5), 1.77 (3H, br s, $CH_3C$=C), 1.69 (1H, ddd, *J* = 3, 4, 13 Hz, HC-5), 1.47 (1H, br s, HO), 1.37 (3H, s, $H_3CC$-7b), 1.35 (1H, ddd, *J* = 12.5, 13, 13.5 Hz, HC-7), 0.87 (3H, s, $H_3CC$-3a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 208.5 (s, C-2), 149.0 (s, C=$CH_2$), 109.7 (t, $CH_2$=C), 74.5 (d, C-4), 66.2 (s, C-7b), 62.9 (d, C-1a), 47.6 (t, C-3), 44.4 (s, C-3a), 40.6 (d, C-6 or C-7a), 39.4 (d, C-7a or C-6), 33.9 (t, C-5), 29.2 (t, C-7), 21.1 ($CH_3C$-7b), 20.7 ($CH_3C$=C), 18.4 ($CH_3C$-3a)

**LRMS** (EI), *m/z* (relative intensity): 250 ([M]$^+$, 4), 232 (10), 190 (13), 175 (15), 153 (100), 135 (20), 107 (31), 93 (19)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1565.

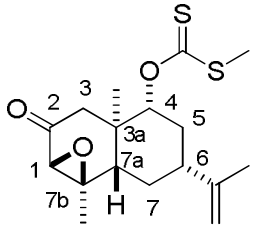
***O*-(1a*R*,3a*R*,*4RS*,6*R*,7a*S*,7b*R*)-decahydro-3a,7b-dimethyl-6-(1-methylethenyl)-2-oxo-naphtho[2,1-b]oxiren-4-yl *S*MethylCarbonodithioate (362).**



**362**

**Procedure:** $NaN(SiMe_3)_2$ (1.0 M in THF; 5.3 mL, 5.3 mmol), $CS_2$ (0.87 mL, 1.1 g, 15 mmol), and MeI (1.50 mL, 3.43 g, 24.2 mmol) were sequentially added to a stirred solution of the above 4:1 mixture of **355b** and **355a** (1.21 g, 4.83 mmol), respectively, in THF (48 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 16 h and then was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated, and the residue was passed over a short pad of silica gel eluting with 20% ethyl acetate in hexane to afford a 4:1 mixture (by 1H NMR) of xanthates (**362**) (1.39 g, 85%) as yellow oil.

***O*-(1a*R*,3a*R*,4*R*,6*R*,7a*S*,7b*R*)-Decahydro-3a,7b-dimethyl-6-(1-methylethenyl)-2-oxo-naphtho[2,1-b]oxiren-4-yl *S*-MethylCarbonodithioate (362a)**



**362b**

**[α]$_D$** –12 (*c* 0.77, $C_6H_6$)

**IR** νmax: 3072, 1711, 1641 $cm^{-1}$

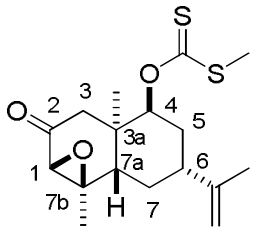
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.57 (1H, dd, *J* = 4.5, 11.5 Hz, HC-4), 4.81 (1H, br s, HC=C), 4.79 (1H, br s, HC=C), 3.05 (1H, s, HC-1a), 2.55 (3H, s, $H_3CS$), 2.44 (1H, d, *J* = 14 Hz, HC-3), 2.25 (1H, d, *J* = 14 Hz, HC-3), 2.24-2.17 (2H, m, HC-6, HC-7a), 2.12 (1H, ddd, *J* = 3.5, 4.5, 13 Hz, HC-5), 1.93 (1H, ddd, *J* = 3.5, 3.5, 13 Hz, HC-7), 1.78 (3H, s, $H_3CC$=C), 1.58 (1H, ddd, *J* = 11.5, 12, 13 Hz, HC-5), 1.40 (3H, s, $H_3CC$-7b), 1.39 (1H, ddd, *J* = 12.5, 13, 13 Hz, HC-7), 1.02 (3H, s, $H_3CC$-3a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 215.9 (s, C=S), 205.8 (s, C-2), 147.4 (S, C=$CH_2$), 110.4 (t, $CH_2$=C), 86.4 (d, C-4), 65.3 (s, C-7b), 62.5 (d, C-1a), 47.2 (t, C-3), 46.8 (d, C-7a), 44.2 (s, C-3a), 42.7 (d, C-6), 30.4 (t, C-5), 28.6 (t, C-7), 21.0 (q, $CH_3C$=C), 20.8 (q, $CH_3C$-7b), 19.2 (q, $CH_3S$), 14.2 (q, $CH_3C$-3a)

**LRMS** (EI), *m/z* (relative intensity): 340 ([M]$^+$, 22), 233 (99), 232 (64), 205 (100), 191 (43), 145 (61), 107 (97), 91 (48)

**HRMS** *m/z* calcd for $C_{17}H_{24}O_3S_2$ 340.1167, found 340.1163 (EI).

***O*-(1a*R*,3a*R*,4*S*,6*R*,7a*S*,7b*R*)-Decahydro-3a,7b-dimethyl-6-(1-methylethenyl)-2-oxo-naphtho-[2,1-b]oxiren-4-yl *S*-MethylCarbonodithioate (362b)**




**362b**

**[α]$_D$** +14 (*c* 2.2, $C_6H_6$)

**IR** νmax: 3070, 1719, 1647 cm$^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.54 (1H, dd, *J* = 3, 3 Hz, HC-4), 4.80 (1H, br s, HC=C), 4.76 (1H, br s, HC=C), 3.04 (1H, d, *J* = 1 Hz, HC-1a), 2.74 (1H, dd, *J* = 1, 14 Hz, HC-3),

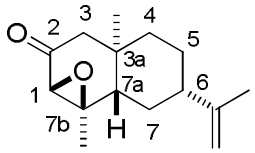
2.67 (1H, dd, *J* = 4, 13 Hz, HC-7a), 2.58 (3H, s, $H_3CS$), 2.34 (1H, dddd, *J* = 4, 4, 13, 13 Hz, HC-6), 2.00-2.10 (2H, m, HC-5, HC-7), 1.92 (1H, d, *J* = 14 Hz, HC-3), 1.77 (1H, ddd, *J* = 3, 13, 15 Hz, HC-5), 1.76 (3H, br s, $H_3CC$=C), 1.41 (1H, ddd, *J* = 13, 13, 13 Hz, HC-7), 1.40 (3H, s, $H_3CC$-7b), 0.98 (3H, s, $H_3CC$-3a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 215.5 (s, C=S), 206.7 (s, C-2), 148.2 (s, C=$CH_2$), 110.2 (t, $CH_2$=C), 85.4 (d, C-4), 65.5 (s, C-7b), 62.7 (d, C-1a), 46.9 (t, C-3), 43.5 (s, C-3a), 42.5 (d, C-7a), 40.3 (d, C-6), 29.9 (t, C-5), 29.0 (t, C-7), 21.0 (q, $CH_3C$=C), 20.6 (q, $CH_3C$-7a), 19.3 (q, $CH_3S$), 18.2 (q, $CH_3C$-3a)

**LRMS** (EI), *m/z* (relative intensity): 340 ([M]$^+$, 1), 265 (1), 232(100), 205 (19), 161 (5), 133 (16), 91 (23), 67 (14)

**HRMS** *m/z* calcd for $C_{17}H_{24}O_3S_2$ 340.1167, found 340.1162 (EI).

**(1a*R*,3a*R*,6*S*,7a*S*,7b*R*)-Octahydro-3a,7b-dimethyl-6-(1-methylethenyl)-naphtho[2,1-b]oxiren-2(1a*H*)-one (363).**




**363**

**Procedure:** $Bu_3SnH$ (1.65 mL, 1.78 g, 6.12 mmol) was added to a stirred solution of the above mixture of xanthates (**362**) (1.39 g, 4.08 mmol) in toluene (41 mL). The reaction mixture was heated under reflux and after 10 min, AIBN (0.100 g) was added. After 10 min, the reaction mixture was concentrated and the residue fractionated by FCC (hexane followed by 10% ethyl acetate in hexane) to afford the title compound (0.87 g, 91%) as a thick oil.

**$[\alpha]_D$** –45 (*c* 1.0, $C_6H_6$)

**IR** νmax: 3090, 1719, 1647 $cm^{-1}$

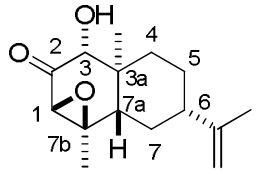
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.76 (2H, br s, $H_2C$=C), 3.01 (1H, s, HC-1a), 2.45 (1H, d, *J* = 14 Hz, HC-3), 2.06 (1H, dd, *J* = 3.5, 13 Hz, HC-7a), 2.01 (1H, dddd, *J* = 4, 4, 13, 13 Hz, HC-6), 1.96 (1H, d, *J* = 14 Hz, HC-3), 1.90 (1H, ddd, *J* = 3.5, 4, 13 Hz, HC-7), 1.77 (3H, s, $H_3CC$=C), 1.65-1.59 (1H, m, HC-5), 1.52-1.36 (3H, m, $H_2C$-4, HC-5), 1.35 (3H, s, $H_3CC$-7b), 1.32 (1H, ddd, *J* = 13, 13, 13 Hz, HC-7), 0.85 (3H, s, $H_3CC$-3a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 207.3 (s, C-2), 149.6 (s, C=$CH_2$), 109.3 (t, $CH_2$=C), 66.3 (s, C-7b), 62.9 (d, C-1a), 52.1 (t, C-3), 48.5 (d, C-7a), 46.2 (d, C-6), 40.0 (s, C-3a), 39.4 (t, C-4), 29.3 (t, C-7), 26.5 (t, C-5), 21.1 (q, $CH_3C$=C), 20.4 (q, $CH_3C$-7b), 17.8 (q, $CH_3C$-3a)

**LRMS** (EI), *m/z* (relative intensity): 234 ([M]$^+$, 94), 219 (100), 191 (15), 161 (11), 121 (21), 107 (31), 95 (94), 79 (28), 67 (37)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1619 (EI).

**(1a*R*,3*R*,3a*S*,6*S*,7a*S*,7b*R*)-Octahydro-3-hydroxy-3a,7bdimethyl-6-(1-methylethenyl)-naphtho[2,1-b]oxiren-2(1a*H*)-one (365)**




**365**

**Procedure:** NaOH (2.5 M in MeOH; 5.0 mL, 13 mmol) and $PhI(OAc)_2$ (0.690 g, 2.14 mmol) were sequentially added to a stirred solution of epoxide **363** (0.250 g, 1.07 mmol) in MeOH (8 mL) at 0 °C. The cooling bath was removed and after 1 h, the reaction was quenched by addition of saturated aq $Na_2S_2O_3$. The mixture was extracted with $CH_2Cl_2$ and the combined organic layers were dried over $Na_2SO_4$ and concentrated to get crude methoxydiepoxide (0.320 g). Aq. HCl (1.2 N; 2.5 mL, 3 mmol) was added to a stirred solution of the crude methoxydiepoxide (0.320 g) in THF (10 mL) at room temperature.

After 10 min, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to afford the title compound (0.230 g, 85%) as an oil.

**$[\alpha]_D$** –45 (*c* 1.2, $C_6H_6$)

**IR** νmax: 3487, 3070, 1712, 1643 $cm^{-1}$

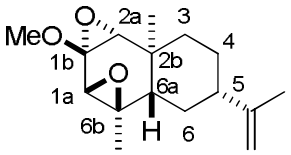
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.77 (2H, br s, $H_2C$=C), 4.15 (1H, d, *J* = 4 Hz, HC-3), 3.38 (1H, d, *J* = 4 Hz, HO), 3.29 (1H, s, HC-1a), 2.17 (1H, dd, *J* = 3, 13 Hz, HC-7a), 2.07-1.99 (1H, m, HC-6), 1.94-185 (2H, m, HC-4, HC-7) , 1.79 (3H, s, $H_3CC$=C), 1.71-1.65 (1H, m, HC-5), 1.40 (3H, s, $H_3CC$-7b), 1.46-1.34 (3H, m, HC-4, HC-5, HC-7), 0.71 (3H, s, $H_3CC$-3a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 207.7 (s, C-2), 149.6 (s, C=$CH_2$), 109.4 (t, $CH_2$=C), 80.2 (d, C-3), 67.8 (s, C-7b), 62.7 (d, C-1a), 47.5 (d, C-7a), 46.5 (s, C-3a), 45.8 (d, C-6), 35.3 (t, C-4), 29.1 (t, C-7), 26.1 (t, C-5), 21.1 (q, $CH_3C$=C), 20.5 (q, $CH_3C$-7b), 11.7 (q, $CH_3C$-3a)

**LRMS** (EI), *m/z* (relative intensity): 250 ($[M]^+$, 26), 232 (11), 217 (46), 163 (21), 147 (45), 121 (51), 107 (100), 93 (80)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1567 (EI).

**(1a*R*,1b*R*,2a*R*,2b*S*,5*S*,6a*S*,6b*R*)-Decahyro-1b-methoxy-2b,6b,-dimethyl-5-(1-methylethenyl)naphtho[1,2-b:3,4-b']bisoxirene (364).**




**364**

The crude methoxyepoxide obtained from oxidation of **363**

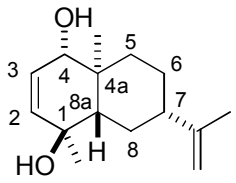
.

**$^{1}$H NMR** (500 MHz, $C_6D_6$) δ: 4.76 (1H, br s, HC=C), 4.71 (1H, br s, HC=C), 3.28 (3H, s, $H_3CO$), 3.14 (1H, d, *J* = 1.5 Hz, HC-1a), 3.08 (1H, d, *J* = 1.5 Hz, HC-2a), 1.65 (1H, dddd, *J* = 2, 3.5, 5, 13 Hz, HC-6), 1.62-1.59 (1H, m, HC-5), 1.57 (3H, br s, $H_3CC$=C), 1.49 (1H, dd, *J* = 4, 13 Hz, HC-6a), 1.36-1.29 (2H, m, HC-3, HC-4), 1.22 (1H, dddd, *J* = 3, 13, 13, 13 Hz, HC-4), 1.06 (1H, ddd, *J* = 13, 13, 13 Hz, HC-6), 0.95 (3H, br s, $H_3CC$-6b), 0.99-0.90 (1H, m, HC-3), 0.73 (3H, s, $H_3CC$-2b)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) δ: 149.9 (s, C=$CH_2$), 109.3 (t, $CH_2$=C), 83.2 (s, C-1b), 67.9 (d, C-2a), 59.0 (s, C-6b), 55.5 (d, C-1a), 52.3 (q, $CH_3O$), 48.7 (d, C-6a), 45.6 (d, C-5), 39.2 (t, C-3), 34.6 (s, C-2b), 29.2 (t, C-6), 27.3 (t, C-4), 21.3 (q, $CH_3C$=C), 19.7 (q, $CH_3C$-6b), 14.8 (q, $CH_3C$-2b)

**HRMS** *m/z* calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1726 (EI).

**(1*S*,4*S*,4a*S*,7*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-1,4adimethyl-7-(1-methylethenyl)-naphthaalene-1,4-diol (366)**




**366**

**Procedure:** $H_2NNH_2 \cdot H_2O$ (0.077 mL, 0.080 g, 1.6 mmol) was added to a stirred solution of **365** (0.200 g, 0.799 mmol) in MeOH (8 mL) at 0 °C. After 15 min, acetic acid (0.092 mL, 0.088 g, 1.6 mmol) was added and the cooling bath was removed. After 1 h, the reaction was quenched by addition of saturated aq $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$ and the combined organic layers were dried over $Na_2SO_4$, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to afford the title compound (0.170 g, 90%) as a white foam.

**$[\alpha]_D$** +19 (*c* 0.34, $C_6H_6$)

**IR** νmax: 3358, 3079, 3025, 1632 $cm^{-1}$

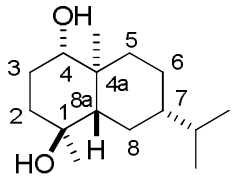
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.57 (2H, ap s, HC-2, HC-3), 4.74 (2H, ap s, $H_2C$=C), 3.99 (1H, br s, HC-4), 2.00-1.91 (3H, m, HC-5, HC-7, HC-8), 1.77 (3H, s, $H_3CC$=C), 1.68-1.63 (1H, m, HC-6), 1.61 (1H, dd, *J* = 3, 12.5 Hz, HC-8a), 1.41-1.25 (3H, m, HC-5, HC-6, HC-8), 1.18 (3H, s, $H_3CC$-1), 0.90 (3H, s, $H_3CC$-4a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 150.5 (s, C=$CH_2$), 135.2 (d, C-2), 130.5 (d, C-3), 108.6 (t, $CH_2$=C), 78.2 (d, C-4), 71.3 (s, C-1), 51.3 (d, C-8a), 45.7 (d, C-7), 40.1 (s, C-4a), 39.5 (t, C-5), 27.3 (t, C-8), 26.9 (t, C-6), 21.3 (q, $CH_3$C-1), 21.3 (q, $CH_3$C=C), 13.0 (q, $CH_3$C-4a)

**LRMS** (EI), *m/z* (relative intensity): 236 ($[M]^+$, 21), 221 (74), 203 (52), 179 (92), 161 (100), 147 (53), 135 (50)

**HRMS** *m/z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1764 (EI).

**(1*S*,4*S*,4a*S*,7*S*,8a*S*)-Decahydro-1,4a-dimethyl-7-(1-methylethyl)naphthalene-1,4-diol (dihydrolairdinol A, 367).**




**367**

**Procedure:** A stirred suspension of **366** (0.025 g, 0.11 mmol) and 10 % Pd/C (3 mg) in MeOH (1.5 mL) was evacuated and $H_2$ gas was introduced using a balloon. After 1 h, the reaction mixture was passed through pad of Celite®. The combined filtrate and washings were concentrated and fractionated by PTLC (50% ethyl acetate in hexane) to afford the title compound (0.024 g, 95 %) as a white foam.

**$[\alpha]_D$** +12 (*c* 0.9, $C_6H_6$)

**IR** νmax: 3381 $cm^{-1}$

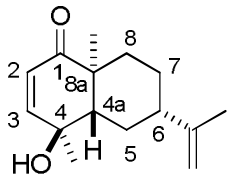
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 3.31 (1H, dd, *J* = 4, 11 Hz, HC-4), 1.88-1.83 (1H, m, HC-5), 1.82-1.74 (2H, m, HC-2, HC-8), 1.74-1.69 (1H, m, HC-3), 1.66-1.40 (4H, m, HC-2, HC-3, HC-6, HCC-7), 1.21 (1H, ap dd, *J* = 3, 12 Hz, HC-8a), 1.17-1.00 (4H, m, HC-5, HC-6, HC-7, HC-8), 1.12 (3H, s, $H_3$CC-1), 0.90 (3H, d, *J* = 7 Hz, $H_3$CCH), 0.89 (3H, d, *J* = 7 Hz, $H_3$CCH), 0.86 (3H, s, $H_3$CC-4a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 79.8 (d, C-4), 72.0 (s, C-1), 53.2 (d, C-8a), 44.7 (d, C-7), 41.2 (t, C-2), 40.9 (t, C-5), 39.9 (s, C-4a), 33.3 (d, CHC-7), 28.8 (t, C-3), 24.7 (t, C-6), 24.1 (t, C-8), 22.9 (q, $CH_3$C-1), 20.2 (q, $CH_3$CH), 20.0 (q, $CH_3$CH), 13.2 (q, $CH_3$C-4a)

**LRMS** (EI), *m/z* (relative intensity): 240 ($[M]^+$, 3), 181 (46), 164 (21), 123 (12), 107 (16), 95 (76), 72 (100), 55 (63)

**HRMS** *m/z* calcd for $C_{15}H_{28}O_2$ 240.2089, found 240.2083 (EI).

**(4*S*,4a*S*,6*S*,8a*S*)-4a,5,6,7,8,8a-Hexahydro-4-hydroxy-4,8adimethyl-6-(1-methyleth-enyl)naphthaalen-1(4*H*)-one (369).**




**369**

**Procedure:** Dess-Martin periodinane (0.457 g, 1.08 mmol) was added to a stirred solution of **366** (0.170 g, 0.720 mmol) in dry $CH_2Cl_2$ (8 mL) at room temperature. After 20 min, the reaction was quenched by addition of a 1:1 mixture (v/v) of saturated aq $Na_2S_3O_4$ and saturated aq. $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$ and the combined organic layers were dried over $Na_2SO_4$, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to afford the title compound (0.154 g, 91%) as a white foam.

**$[\alpha]_D$** +16, (*c* 0.59, $C_6H_6$)

**IR** νmax: 3439, 3084, 1681 $cm^{-1}$

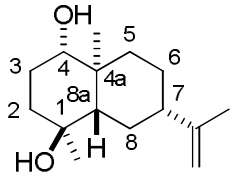
**$^1$H NMR** (500 MHz, $CDCl_3$) δ:6.64 (1H, d, *J* = 10 Hz, HC-3), 5.85 (1H, d, *J* = 10 Hz, HC-2), 4.75 (2H, br s, $H_2C$=C), 2.03-1.88 (4H, m, HC-4a, HC-5, HC-6, HC-8), 1.77 (3H, s, $H_3CC$=C), 1.76-1.70 (1H, m, HC-8), 1.50-1.36 (3H, m, HC-5, $H_2C$-7), 1.33 (3H, s, $H_3CC$-4), 1.13 (3H, s, $H_3CC$-8a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 204.8 (s, C-1), 153.8 (d, C-3), 149.9 (s, C=$CH_2$), 125.8 (d, C-2), 109.0 (t, $CH_2$=C), 70.8 (s, C-4), 52.3 (d, C-4a), 45.2 (d, C-6), 44.9 (s, C-8a), 35.0 (t, C-5), 26.6 (t, C-7 of C-8), 26.5 (t, C-7 orC-8), 22.5 (q, $CH_3$C-4), 21.3 (q, $CH_3$C=C), 18.3 (q, $CH_3$C-8a)

**LRMS** (EI), *m/z* (relative intensity): 234 ([M]$^+$, 42), 179 (22), 152 (20), 125 (36), 98 (100), 81 (14), 54 (15)

**HRMS** *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1621 (EI).

**(1*S*,4*S*,4a*S*,7*S*,8a*S*)-Decahydro-1,4a-dimethyl-7-(1-methylethenyl)naphthalene-1,4-diol (lairdinol A, 51).**




**51**

**Procedure:** $PhMe_2SiH$ (0.049 mL, 0.044 g, 0.32 mmol) was added to a stirred solution of $[CuH(PPh_3)]_6$ (0.021 g, 0.011 mmol, weighed in glove box) in toluene (1.5 mL) at room temperature under argon. After 5 min, a solution of enone **369** (0.050 g, 0.21 mmol) in toluene (0.5 mL) was added to the reaction mixture. After 48 h, the reaction mixture was concentrated [note: fractionation of the residue by FCC (50% ethyl acetate in hexane) at this juncture gave the ketone **370** in 88% yield]. The residue was taken up in MeOH (3 mL) and $NaBH_4$ (25 mg, 0.63 mmol) was added with stirring at 0 °C. After 10 min, the mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to afford **51** (0.046 g, 91%) as a white solid. Similar reduction of the purified **370** gave **51** in 98% yield.

**[α]$_D$** +18 (*c* 0.4, $CH_2Cl_2$), +34 (*c* 1.1, MeOH), +28 (*c* 1.3, $CHCl_3$) [lit.[19] +18 (c 0.4 $CH_2Cl_2$); lit.[42, 43] for *ent*-**51** (cyperusol C) –42.3 (*c* 1.10, MeOH),[42] –25 (*c* 0.13, $CHCl_3$)[43]]

**IR** νmax: 3387, 3070, 1644 cm$^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) δ:[†] 4.86 (1H, br s, HC=C), 4.83 (1H, br s, HC=C), 2.99 (1H, dd, *J* = 4.5, 11 Hz, HC-4), 1.93 (1H, dddd, *J* = 2, 2, 4, 13 Hz, HC-8), 1.89-1.82 (1H, m, HC-7), 1.83 (1H, ddd, *J* = 3, 3.5, 12.5 Hz, HC-5), 1.71 (3H, s, $H_3CC$=C), 1.58-1.52 (2H, m, HC-2, HC-6), 1.46-1.30 (3H, m, $H_2C$-3, HC-6), 1.26 (1H, ddd, *J* = 4.5, 13, 13 Hz, HC-2), 1.19 (1H, ddd, *J* = 12, 12.5, 12.5 Hz, HC-8), 1.03 (1H, dd, *J* = 2.5, 12.5 Hz, HC-8a), 0.93 (1H, ddd, *J* = 3, 13, 13 Hz, HC-5), 0.90 (3H, s, $H_3CC$-1), 0.76 (3H, s, $H_3CC$-4a)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ:[¶] 4.73-4.71 (2H, m, $H_2C$=C), 3.34 (1H, dd, *J* = 4, 11 Hz, HC-4), 1.94 (1H, dddd, *J* = 3.5, 3.5, 11.5, 11.5 Hz, HC-7), 1.90 (1H, ddd, *J* = 3.5, 3.5, 12.5 Hz, HC-5), 1.87-1.83 (1H, m, HC-8), 1.81 (1H, ddd, *J* = 3.5, 3.5, 12.5 Hz, HC-2), 1.76 (3H, s, $H_3CC$=C), 1.74 (1H, m, HC-3), 1.66-1.56 (2H, m, HC-3, HC-6), 1.52 (1H, ddd, *J* = 3.5, 13.5, 13.5 Hz, HC-2), 1.38 (1H, dddd, *J* = 3.5, 13, 13.5, 17 Hz, HC-6), 1.32-1.24 (2H, m, HC-8, HC-8a), 1.16 (1H, ddd, *J* = 4, 13, 13 Hz, HC-5), 1.14 (3H, s, $H_3CC$-1), 0.90 (3H, s, $H_3CC$-4a)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) δ: 150.8 (s, C=$CH_2$), 109.1 (t, $CH_2$=C), 79.7 (d, C-4), 71.3 (s, C-1), 53.6 (d, C-8a), 46.6 (d, C-7), 41.8 (t, C-2), 41.2 (t, C-5), 39.5 (s, C-4a), 29.5 (t, C-3), 27.3 (t, C-6), 26.5 (t, C-8), 23.1 (q, $CH_3$C-1), 21.5 (q, $CH_3$C=C), 13.5 (q, $CH_3$C-4a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 150.5 (s, C=$CH_2$), 108.6 (t, $CH_2$=C), 79.6 (d, C-4), 71.8 (s, C-1), 53.2 (d, C-8a), 45.9 (d, C-7), 41.1 (t, C-2), 40.8 (t, C-5), 39.2 (s, C-4a), 28.8 (t, C-3), 26.6 (t, C-6), 26.0 (t, C-8), 23.0 (q, $CH_3$C-1), 21.2 (q, $CH_3$C=C), 13.3 (q, $CH_3$C-4a)

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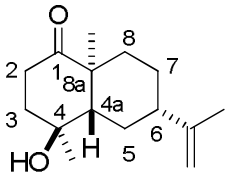
[†] NMR spectra in $C_6D_6$ were essentially superimposable with those kindly provided by Prof. Pedras. However, compared to the reported values, the chemical shifts reported here are consistently different ($\delta_H$, –0.11; $\delta_C$, +0.2) due to a different assignment of the reference frequency (I used $\delta_H$ = 7.16 for $C_6\underline{H}D_5$ and $\delta_C$ = 128.39 for $\underline{C}_6D_6$). Also, two typographical errors were identified in previously reported $\delta_H$s: 1.85 should be 1.95 (or 1.83 using $\delta_H$ = 7.16 for $C_6\underline{H}D_5$); 1.65 should be 1.55 (or 1.43 using $\delta_H$ = 7.16 for $C_6\underline{H}$ $D_5$)

[¶] $^1$H chemical shifts are essentially identical to those reported by Xu *et al.*;(ref. 25) however, the $^{13}$C chemical shifts reported herein are consistently higher by 0.3 ppm presumably due to a different assignment of the reference frequency (I used $\delta_C$ = 77.23 for $\underline{C}$DCl3).

**LRMS** (EI), *m/z* (relative intensity): 238 ([M]$^+$, 2), 220 (4), 202 (3), 179 (5), 162 (7), 101 (7), 84 (100), 72 (16), 56 (12)

**HRMS** *m/z* calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1940 (EI).

**(4*S*,4a*S*,6*S*,8a*S*)-Octahydro-4-hydroxy-4,8a-dimethyl-6-(1-methylethenyl)naphthalen-1(2*H*)-one (370)**




**370**

**[α]$_D$** +16 (*c* 0.67, $C_6H_6$)

**IR** νmax: 3467, 3070, 1701, 1632 cm$^{-1}$

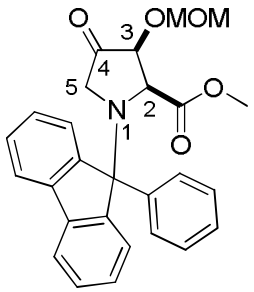
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.73 (2H, br s, $H_2C$=C), 2.60 (1H, ddd, *J* = 5, 10.5, 15.5 Hz, HC-2), 2.44 (1H, ddd, *J* = 5, 7, 15.5 Hz, HC-2), 2.05 (1H, ddd, *J* = 5, 7, 14 Hz, HC-3), 1.96-1.84 (4H, m, HC-3, HC-5, HC-6, HC-7), 1.80 (1H, dd, *J* = 2.5, 12.5 Hz, HC-4a), 1.76 (3H, s, $H_3$CC=C), 1.71-1.67 (1H, m, HC-8), 1.46-1.36 (3H, m, HC-5, HC-7, HC-8), 1.34 (3H, s, $H_3$CC-4), 1.13 (3H, s, $H_3$CC-8a)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 215.9 (s, C-1), 150.0 (s, C=$CH_2$), 108.9 (t, $CH_2$=C), 71.2 (s, C-4), 52.8 (d, C-4a), 46.3 (s, C-8a), 45.6 (d, C-6), 40.1 (t, C-3), 35.7 (t, C-5), 35.4 (t, C-2), 26.8 (t, C-7), 26.5 (t, C-8), 24.3 (q, $CH_3$C-4), 21.3 (q, $CH_3$C=C), 18.1 (q, $CH_3$C-8a)

**LRMS** (EI), *m/z* (relative intensity): 236 ([M]$^+$, 64), 218 (11), 179 (26), 149 (29), 123 (49), 99 (100), 81 (90), 67 (46)

**HRMS** *m/z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1781 (EI).

**Methyl (2*S*,3*S*)-3-(Methoxymethoxy)-4-oxo-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate [Pf-(4-oxo)(3-OMOM)Pro-OMe] (170)**[62]




**170**

**Procedure:** *N*,*N*-Dimethylaniline (1.9 mL, 1.8 g, 15 mmol) and MOM-Cl (0.81 mL, 0.86 g, 11 mmol) were sequentially added to a stirred solution of **169** (0.85 g, 2.1 mmol) in $CH_2Cl_2$ (8.5 mL) at room temperature under argon. After 1 day, the reaction mixture was diluted with diethyl ether and washed with 10% aq. HCl, sat. $NaHCO_3$. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to afford the title compound as a pale yellow foam (0.75 g, 80%).

**$[\alpha]_D$** –176 (*c* 1.1, $CHCl_3$) [lit.[62] -158.2 (*c*1.1, $CHCl_3$)]

**IR** $\nu_{max}$ 1767, 1731 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) 7.75 (1H, ddd, *J* = 1, 1, 7.5 Hz, Pf), 7.69 (1H, dd, *J* = 1, 8 Hz, Pf), 7.44 (1H, dd, *J* = 1, 7.5 Hz, Pf), 7.43-7.35 (5H, m, Pf), 7.33 (1H, ddd, *J* = 1, 7.5, 8 Hz, Pf), 7.30-7.23 (4H, m, Pf), 4.65 (1H, d, *J* = 6.5 Hz, $H_2CO_2$), 4.57 (1H, d, *J* = 6.5 Hz, $H_2CO_2$), 4.49 (1H, dd, *J* = 1, 7.5 Hz, HC-3), 3.98 (1H, d, *J* = 7.5 Hz, HC-2), 3.90 (1H, d, *J* = 17.5 Hz, HC-5), 3.60 (1H, dd, *J* = 1, 17.5 Hz, HC-5), 3.30 (3H, s, $H_3COC$=O), 3.11 (3H, s, $H_3CO$). [lit.[62] 1H NMR ($CD_2Cl_2$) δ 3.06 (s, 3H), 3.24 (s, 3H), 3.57 (d, *J* = 17.2 Hz, 1H), 3.86 (d, *J* = 17.3 Hz, 1H), 3.93 (d, *J* = 7.7 Hz, 1H), 4.47 (d, *J* = 7.8 Hz, 1H), 4.52 (d, *J* ) 6.7 Hz, 1H), 7.24-7.48 (m, 13H)]

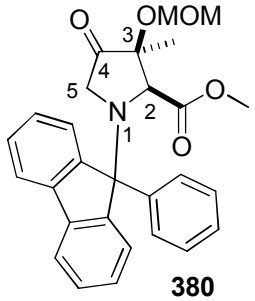
**$^{13}$C NMR** (125 MHz, $CDCl_3$) 209.3 (s, C-4), 170.7 (s, OC=O), 146.6 (s, Pf), 144.9 (s, Pf), 141.6 (s, Pf), 141.2 (s, Pf), 139.9 (s, Pf), 129.23 (d, Pf), 129.19 (d, Pf), 128.9 (dx2,

Pf), 128.3 (d, Pf), 128.1 (d, Pf), 127.7 (d, Pf), 126.9 (d x2, Pf), 125.5 (d, Pf), 120.4 (d, Pf), 120.4 (d, Pf), 96.5 (t, $CH_2O_2$), 77.7 (d, C-3), 75.1, 61.4 (d, C-2), 56.2 (q, $CH_3O$), 52.2 (t, C-5), 51.4 (q, $CH_3OC{=}O$) [lit.[62] $^{13}C$ NMR ($CD_2Cl_2$) δ 51.5, 52.6, 56.2, 61.7, 75.6, 78.3, 97.1,120.7, 120.8, 125.9, 127.3, 127.4, 128.1, 128.4, 128.6, 128.4,128.6, 129.2, 129.5, 129.6, 140.5, 141.9, 145.6, 147.3, 171.1, 209.3].

**LRMS** (EI), *m/z* (relative intensity): 443 ($[M]^+$, 3), 242 (30), 241 (100), 139 (16).

**HRMS** *m/z* calcd for $C_{27}H_{25}NO_5$ 443.1733, found 443.1717 (EI).

**(2*S*,3*S*)-methyl-3-(methoxymethoxy)-3-methyl-4-oxo-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate (380)**




**380**

**Procedure:** DMPU (5 mL) was added to a stirred solution of $KN(SiMe_3)_2$ (0.45 M in toluene; 3.0 mL, 1.4 mmol) in 5 mL toluene at 0 °C. After 10 min, the mixture was cooled to -78 °C and a solution of proline ester **170** (0.60 g, 1.4 mmol) in toluene and DMPU (1:1 (v/v); 8 mL). After 1 h, $CH_3I$ (0.84 mL, 1.9 g, 1.4 mmol) was added via syringe. After 2 h, the reaction was quenched by addition of $KH_2PO_4$ (1 M; 20 mL). The mixture was allowed to warm to ambient temperature and then was extracted with ethyl acetate. The combined organic layers were washed sequentially with $H_2O$ and brine, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (gradient elution; 10-20% ethyl acetate in hexane) to afford the diastereomer **381** (0.093 g, 15%) and a 8:1 mixture of the title compound **380** and the enol ether **382** (0.42 g, 68%) as a white foam.

**IR** $\nu_{max}$: 3065, 1762, 1738, 1020, 733 $cm^{-1}$.

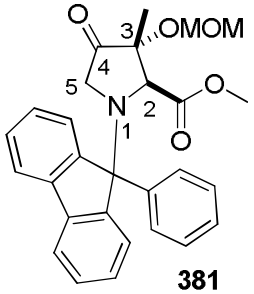
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.75 (1H, d, *J* = 7.5 Hz, Ar), 7.70 (1H, d, *J* = 7.5 Hz, Ar), 7.21-7.47 (11H, m, Ar), 4.91 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.63 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.08 (1H, d, *J* = 17.5 Hz, HC-5), 3.72 (1H, d, *J* = 17.5 Hz, HC-5), 3.58 (1H, s, HC-2), 3.24 (3H, s, $H_3CO$), 3.00 (3H, s, $H_3COC{=}O$), 1.68 (3H, s, $H_3CC$-3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 211.1 (s, C-4), 170.8 (s, $COOCH_3$), 146.4, 144.8, 141.5, 141.4, 140.1, 129.2, 129.1, 129.0, 128.3, 128.0, 127.5, 127.4, 126.9, 125.5, 120.50, 120.46, 92.8 (t, $OCH_2O$), 81.7, 74.8 (s, C-3), 68.7 (d, C-2), 56.0 (q, $CH_3O$), 52.1 (t, C-5), 51.1 (q, $CH_3OC{=}O$), 20.7 (q, $CH_3C$-3).

**LRMS** (EI), *m/z* (relative intensity):457 ($[M]^+$, 2), 242 (23), 241 (100), 239 (18), 184 (2).

**HRMS** *m/z* calcd for $C_{28}H_{27}NO_5$ 457.1889, found 457.1889.

**(2*S*,3*R*)-Methyl-3-(methoxymethoxy)-3-methyl-4-oxo-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate (381)**




**381**

**$[\alpha]_D$** –85 (c 0.83, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3056, 1765, 1732, 1011, 726 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.74 (1H, d, *J* = 7.5 Hz, Ar-H), 7.70 (1H, d, *J* = 7.5 Hz, Ar-H), 7.22-7.52 (11H, m, Ar-H), 4.92 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.67 (1H, d, *J* = 7 Hz,

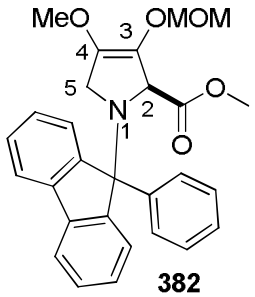
$OCH_2O$), 3.94 (1H, d, *J* = 17.5 Hz, HC-5), 3.88 (1H, d, *J* = 17.5 Hz, HC-5), 3.79 (1H, s, HC-2), 3.40 (3H, s, $H_3CO$), 3.03 (3H, s, $H_3COC{=}O$), 1.08 (3H, s, $H_3CC$-3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 209.4 (s, C-4), 171.5 (s, $COOCH_3$), 146.5, 145.3, 141.7, 141.4, 140.1, 129.1, 128.9, 128.8, 128.1, 127.8, 127.47, 127.44, 127.2, 126.1, 120.32, 120.30, 92.4 (t, $OCH_2O$), 80.2, 75.0 (s, C-3), 68.9 (d, C-2), 56.1 (q, $CH_3O$), 53.0 (t, C-5), 51.2 (q, $CH_3OC{=}O$), 15.7 (q, $CH_3C$-3).

**LRMS** (EI), *m/z* (relative intensity):457 ($[M]^+$, 3), 258 (14), 242 (37), 241 (100), 181 (10), 152 (3), 77 (1).

**HRMS** *m/z* calcd for $C_{28}H_{27}NO_5$ 457.1889, found 457.1895.

**(*S*)-Methyl-4-methoxy-3-(methoxymethoxy)-1-(9-phenyl-9*H*-fluoren-9-yl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (382)**




**382**

**[α]$_D$** +86 (c 0.62, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3065, 1743, 1068, 739, 697 $cm^{-1}$

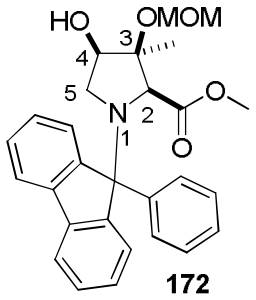
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.73 (1H, ddd, *J* = 1, 1, 7.5 Hz, Pf), 7.64 (1H, ddd, *J* = 1, 1, 7.5 Hz, Pf), 7.51-7.57 (3H, m, Pf), 7.44 (1H, ddd, *J* = 1, 1, 7.5 Hz, Pf), 7.42 (1H, ddd, *J* = 1, 7.5, 7.5 Hz, Pf), 7.32 (1H, ddd, *J* = 1, 7.5, 7.5 Hz, Pf), 7.29 (1H, ddd, *J* = 1, 7.5, 7.5 Hz, Pf), 7.22-7.28 (3H, m, Pf), 7.17 (1H, ddd, *J* = 1, 7.5, 7.5 Hz, Pf), 4.74 (1H, d, *J* = 6

Hz, $OCH_2O$), 4.66 (1H, d, *J* = 6 Hz, $OCH_2O$), 4.03 (1H, dd, *J* = 6.5, 13 Hz, HC-5), 3.85 (1H, dd, *J* = 2.5, 6 Hz, HC-2), 3.63 (1H, dd, *J* = 2.5, 13 Hz, HC-5), 3.61 (3H, s, $H_3COC=O$), 3.45 (3H, s, $H_3COC=C$), 3.20 (3H, s, $H_3CO$) .

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 174.2 (s, C=O), 147.7 (s, C-3), 146.6 (s, C-4), 142.6 (s, Pf), 141.7 (s, Pf), 139.9 (s, Pf), 136.6 (s, Pf), 128.9 (d, Pf), 128.7 (d, Pf), 128.6 (d, Pf), 128.2 (d, Pf), 127.7 (d, Pf), 127.6 (d, Pf), 126.6 (d, Pf), 126.2 (d, Pf), 126.1 (s, Pf), 120.3 (d, Pf), 120.1 (d, Pf), 96.1 (t, $OCH_2O$), 77.2 (s, Pf), 65.2 (d, C-2), 58.0 (q, $CH_3OC=O$), 56.7 (q, $CH_3O$), 51.9 (q, $CH_3OC=C$), 51.7 (t, C-5).

**HRMS** *m/z* calcd for $C_{28}H_{27}NO_5$ 457.1889 (458.1962 for M+1), found 458.1965 (CI+).

**(2*S*,3*S*,4*R*)-Methyl-4-hydroxy-3-(methoxymethoxy)-3-methyl-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate (172)**[62]




**172**

**Procedure:** $NaBH_4$ (0.35 g, 0.92 mmol) was added to a stirred solution of an 8:1 mixture of **380** and **382** (0.42 g, 0.092 mmol) in a mixture of $CH_2Cl_2$ and MeOH (1:1 (v/v); 9 mL) at -78 °C under argon. After 16 h, the reaction was quenched by dropwise addition of acetone (5 mL). The mixture was diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (30 % ethyl acetate in hexane) to afford **382** (0.046 g, 11%), diastereomer of **172** at C-4 (0.029 g, 8%), and the title compound **172** as a white foam (0.32 g, 86%).

**IR:** $\nu_{max}$ 3427, 3051, 1722, 1027, 737 $cm^{-1}$.

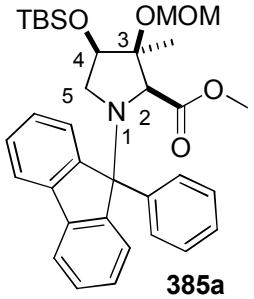
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ: 7.82 (1H, d, *J* = 8 Hz, Ar), 7.67 (1H, d, *J* = 8 Hz, Ar), 7.60-7.64 (2H, m, Ar), 7.47-7.53 (2H, m, Ar), 7.38 (1H, dd, *J* = 8, 8 Hz, Ar), 7.31-7.36 (2H, m, Ar), 7.26-7.31 (4H, m, Ar), 7.14 (1H, dd, *J* = 8, 8 Hz, Ar), 4.74 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.64 (1H, d, *J* = 12 Hz, HO), 4.60 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 3.81 (1H, dd, *J* = 3.5, 12 Hz, HC-4), 3.53 (1H, d, *J* = 10.5 Hz, HC-5), 3.38 (3H, s, $H_3COC$=O), 3.29 (3H, s, $H_3CO$), 3.21 (1H, dd, *J* = 3.5, 10.5 Hz, HC-5), 2.83 (1H, s, HC-2), 0.89 (3H, s, $H_3CC$-3) [lit.[62] 1H NMR ($CD_2Cl_2$) δ 0.83 (s, 3H), 2.74 (s, 1H), 3.21 (s, 3H), 3.30 (s, 3H), 3.40 (d, *J* ) 11.4 Hz, 1H), 3.72 (dd, *J* ) 3.3, 11.7 Hz, 1H), 4.43 (d, *J* ) 11.9 Hz, 1H), 4.51 (d, *J* ) 6.9 Hz, 1H), 4.65 (d, *J* ) 6.9 Hz, 1H), 7.08-7.82 (m, 13 H)].

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 176.1 (s, $COOCH_3$), 148.2, 144.7, 142.1, 141.0, 139.4, 129.1, 128.7, 128.6, 127.9, 127.8, 127.7, 127.3, 127.2, 126.5, 120.6, 120.2, 92.8 (t, $OCH_2O$), 83.4 (s, Pf), 75.8 (d, C-4), 75.5 (s, C-3), 69.7 (d, C-2), 55.8 (q, $CH_3O$), 55.0 (t, C-5), 51.9 (q, $CH_3OC$=O), 23.4 (q, $CH_3C$-3) [lit.[62] $^{13}$C NMR ($CD_2Cl_2$) δ 23.4, 52.0, 55.3, 55.8, 70.1, 75.8, 75.9, 83.6, 93.0, 120.4, 120.8, 126.9, 127.4, 127.6, 128.0, 128.1, 128.2, 128.8, 129.0, 129.2, 129.4, 139.8, 141.7, 142.4, 145.2, 148.5, 176.2].

**LRMS** (EI), *m/z* (relative intensity):459 ($[M]^+$, 1), 400 (11), 242 (24), 241 (100), 239 (11), 215 (1), 165 (1).

**HRMS** *m/z* calcd for $C_{28}H_{29}NO_5$ 459.2046, found 459.2044.

**(2*S*,3*S*,4*R*)-Methyl-4-(tert-butyldimethylsilyloxy)-3-(methoxymethoxy)-3-methyl-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate (385a)**




**385a**

**Procedure:** 2,6-Lutidine (0.15 mL, 0.14 g, 1.4 mmol) and TBSOTf (0.23 mL, 0.27 g, 1.0 mmol) were sequentially added to a stirred solution of alcohol **172** (0.31 g, 0.67 mmol) in dry $CH_2Cl_2$ (6.5 mL) at 0 °C. After 15 min, the mixture was diluted with ethyl acetate and washed sequentially with sat. $NaHCO_3$, 5% aq. HCl, sat. $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (20 % ethyl acetate in hexane) to afford the title compound **385a** (0.36 g, 93%) as a white foam.

**$[\alpha]_D$** +176 (c 0.78, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3056, 1756, 1027 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.75 (1H, dd, *J* = 1, 7.5 Hz, Ar), 7.54-7.66 (2H, m, Ar), 7.45-7.50 (2H, m, Ar), 7.33 (1H, ddd, *J* = 1, 7.5, 8.5 Hz, Ar), 7.19-7.31 (6H, m, Ar), 7.07 (1H, ddd, *J* = 0.5, 7.5, 8 Hz, Ar), 5.12 (1H, d, *J* = 8 Hz, $OCH_2O$), 4.56 (1H, d, *J* = 8 Hz, $OCH_2O$), 3.46-3.54 (2H, m, HC-4 & 5), 3.44 (3H, s, $H_3COC$=O), 3.23-3.32 (1H, m, HC-5), 3.21 (3H, s, $H_3CO$), 2.78 (1H, s, HC-2), 1.14 (3H, s, $H_3CC$-3), 0.84 (9H, s, $(CH_3)_3C$), 0.008 (3H, s, $H_3CSi$),-0.004 (3H, s, $H_3CSi$).

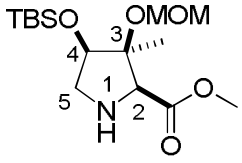
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 172.2 (s, $COOCH_3$), 147.6, 146.4, 143.6, 142.6, 139.2, 129.2, 128.59, 128.56, 128.4, 128.0, 127.7, 127.5, 127.1, 125.6, 120.3, 119.8, 92.6 (t, $OCH_2O$), 83.1 (s, Pf), 77.8 (s, C-3), 77.5 (d, C-4), 70.7 (d, C-2), 55.1 (q, $CH_3O$), 54.3 (t,

C-5), 51.3 (q, $CH_3OC$=O), 25.8 (q, $(CH_3)_3C$), 20.0 (q, $CH_3C$-3), 18.0 (s, $C(CH_3)_3$),-4.3 (q, $CH_3Si$),-4.6 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):573 ($[M]^+$, 0.3), 514 (10), 242 (22), 241 (100), 89 (1), 73 (3).

**HRMS** *m/z* calcd for $C_{34}H_{43}NO_5Si$ 573.2911, found 573.2932.

**(2*S*,3*S*,4*R*)-Methyl-4-(*t*-butyldimethylsilyloxy)-3-(methoxymethoxy)-3-methyl-pyrrolidine-2-carboxylate (388a)**




**388a**

**Procedure:** A stirred suspension of compound **387a** (0.36 g, 0.63 mmol) and 10 % Pd/C (0.14 g) in $^i$PrOH (6 mL) was evacuated and $H_2$ gas was introduced using a balloon. After 6 h, the reaction mixture was passed through pad of Celite® and the combined filtrate and $CH_2Cl_2$ washings were concentrated and fractionated by FCC (5% MeOH in $CH_2Cl_2$) to afford the title compound **388a** (0.18 g, 87%) as a pale yellow oil.

**$[\alpha]_D$** –46 (c 0.81, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1750, 1642, 1026 $cm^{-1}$.

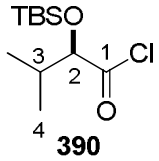
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.17 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.61 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 3.99 (1H, dd, *J* = 7.5, 9.5 Hz, HC-4), 3.80 (3H, s, $H_3COC$=O), 3.91 (1H, s, HC-2), 3.28 (3H, s, $H_3CO$), 3.05 (2H, m, 2XHC-5), 1.94 (1H, br s, HN), 1.55 (3H, s, $H_3CC$-3), 0.89 (9H, s, $(H_3C)_3C$), 0.088 (3H, s, $H_3CSi$), 0.056 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 172.0 (s, $COOCH_3$), 92.6 (t, $OCH_2O$), 82.3 (s, C-3), 79.7 (d, C-4), 68.6 (d, C-2), 55.2 (q, $CH_3O$), 52.3 (q, $CH_3OC{=}O$), 50.3 (t, C-5), 25.9 (q, $(CH_3)_3C$), 18.8 (q, $CH_3C$-3), 18.2 (s, $C(CH_3)_3$),-4.4 (q, $CH_3Si$),-4.8 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):333 ($[M]^+$, 2), 288 (100), 244 (26), 185 (14), 156 (45), 130 (23), 89 (18), 73 (80).

**HRMS** *m/z* calcd for $C_{15}H_31NO_5Si$ 333.1971, found 333.1973.

**(*R*)-2-(*t*-Butyldimethylsilyloxy)-3-methylbutanoyl chloride (390)**



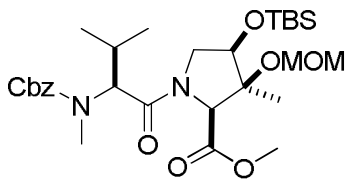

**390**

**Procedure:** Oxalyl chloride (0.013 mL, 0.018 g, 0.15 mmol) was added dropwise to a solution of Bis-TBS-acid **389** (0.034 g, 0.098 mmol) and DMF (ca. 1 μL, 0.01 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C under argon. After 0.5 h, the mixture was allowed to warm to ambient temperature. After 4 h, the mixture was diluted with dry hexane (5 mL) and the resulting solid was removed by filtration. The combined filtrate and hexane washings were concentrated to give the crude acid chloride as a pale yellow oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.19 (1H, d, *J* = 4 Hz, HC-2), 2.24-2.37 (1H, m, HC-3), 1.01 (3H, d, *J* = 6.5 Hz, $H_3C$-4), 0.94 (3H, d, *J* = 6.5 Hz, $H_3C$-4'), 0.93 (9H, s, $(H_3C)3C$), 0.090 (3H, s, $H_3CSi$), 0.070 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 176.3 (s, C-1), 84.4 (d, C-2), 32.2 (d, C-3), 25.8 (q, $(CH_3)_3C$), 19.4 (q, C-4), 18.4 (s, $C(CH_3)3$), 16.2 (q, C-4'), -4.8 (q, $CH_3Si$), -5.2 (q, $CH_3Si$).

**Cbz-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OMe (391a)**




**391a**

**Procedure:** PyBroP (0.38 g, 0.81 mmol) and DIPEA (0.19 mL, 0.14 g, 1.1 mmol) were sequentially added to a stirred solution compound **388a** (0.18 g, 0.54 mmol) and Cbz-MeVal-OH (**60**) (0.19 g, 0.70 mmol) in $CH_2Cl_2$ (5.5 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and then for 18 h at room temperature. The mixture was diluted with $CH_2Cl_2$, washed sequentially with aqueous citric acid (0.5 M) and saturated aqueous $NaHCO_3$, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give the title compound **391a** (0.27 g, 87 %) as a white solid.

**$[\alpha]_D$** –81 (c 1.87, $CH_2Cl_2$)

**IR:** $\nu_{max}$ 1755, 1684, 1648, 1026, 834 $cm^{-1}$.

$^1$**H NMR** (500 MHz, $CDCl_3$) (an ca. 5.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.29-7.39 (5H, m, Ph), 5.35* (d, *J* = 13 Hz), 5.13 (s), 5.04* (2H, d, *J* = 13 Hz, $H_2CPh$), 5.18 (d, *J* = 7.5 Hz), 5.11* (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.61 (d, *J* = 7.5 Hz), 4.60* (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.55 (1H, d, *J* = 11 Hz, Val-HC-2), 4.40 (1H, d, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.28 (1H, s, Pro-HC-2), 3.72-3.80 (4H, m, $H_3COC$=O & Pro-HC-4), 3.52 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.29 (s), 3.28* (3H, s, $H_3CO$), 2.95 (s), 2.94* (3H, s, $H_3CN$), 2.20-2.36 (1H, m, Val-HC-3), 1.60 (s), 1.56* (3H, s, Pro $H_3CC$-3), 1.04 (d), 1.00* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.80-0.94 (12H, m, Val-$H_3C$-4 & $(H_3C)_3C$), 0.12 (s), 0.041* (3H, s, $H_3CSi$), 0.99 (s),-0.044* (3H, s, $H_3CSi$).

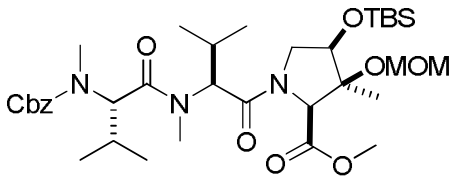
$^{13}$**C NMR** (125 MHz, $CDCl_3$) (an ca. 5.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 170.2 (s, Pro-CO), 169.2* (s, Pro-CO), 167.6 (s, Val CO),

167.4* (s, Val CO), 157.2 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.9 (s, Ph), 136.5* (s, Ph), 128.8* (d, Ph), 128.7 (d, Ph), 128.4* (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 127.6* (d, Ph), 92.77* (t, $OCH_2O$), 92.74 (t, $OCH_2O$), 80.8 (s, Pro-C-3), 80.6* (s, Pro-C-3), 77.0 (d, Pro-C-4), 67.9 (d, Pro-C-2), 67.7* (t, $CH_2Ph$), 67.5 (t, $CH_2Ph$), 62.1* (d, Val-C-2), 61.5 (d, Val-C-2), 55.4* (q, $CH_3O$), 55.3 (q, $CH_3O$), 52.1* (q, $CH_3OC=O$), 52.0 (q, $CH_3OC=O$), 50.1 (t, Pro-C-5), 30.1* (q, $CH_3N$), 29.6 (q, $CH_3N$), 28.0* (d, Val-C-3), 27.9 (d, Val-C-3), 19.60 (q, Pro $CH_3C$-3), 19.56* (q, Pro $CH_3C$-3), 19.3* (q, Val-C-4), 19.0 (q, Val-C-4), 18.9 (q, Val-C-4), 18.8* (q, Val-C-4), 18.1 (s, $C(CH_3)_3$), 18.0* (s, $C(CH_3)_3$),-4.66 (q, $CH_3Si$),-4.69* (q, $CH_3Si$),-4.9* (q, $CH_3Si$),-5.0 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):580 ($[M]^+$, 0.1), 523 (5), 371 (10), 220 (31), 176 (31), 91 (100), 73 (9).

**HRMS** *m/z* calcd for $C_{29}H_{48}N_2O_8Si$ 580.3180, found 580.3174.

**Cbz-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OMe (392a):**




**392a**

**Procedure:** A stirred suspension of **391a** (0.035 g, 0.060 mmol) and 10 % Pd/C (10 mg) in $^i$PrOH (0.6 mL) was evacuated and $H_2$ gas was introduced using a balloon. After 4 h, the reaction mixture was passed through pad of Celite®. The combined filtrate and $CH_2Cl_2$ washings were concentrated to give the crude deprotected amine (0.028 g). PyBroP (0.044 g, 0.094 mmol) and DIPEA (0.022 mL, 0.016 g, 0.12 mmol) were sequentially added to a stirred solution of Z-MeVal-OH (**60**) (0.022 g, 0.081 mmol) and the above crude amine in $CH_2Cl_2$ (1 mL) at 0 °C under argon. After 10 min, the mixture was allowed to warm to ambient temperature. After 18 h, the mixture was diluted with $CH_2Cl_2$, washed sequentially with aqueous citric acid (0.5 M) and saturated aqueous

$NaHCO_3$, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give **392a** (0.035 g, 83 %) as a white solid.

**$[\alpha]_D$** −131 (*c* 0.70, $CH_2Cl_2$)

**IR** $\nu_{max}$ 1765, 1700, 1641 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ 7.37-7.27 (5H, m, Ph), 5.22* (1H, d, *J* = 12 Hz, HCPh), 5.19-5.11 (3H, m, $H_2$CPh & OCHO), 5.08* (3H, d, *J* = 12 Hz, HCPh), 5.00 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.96* (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.72 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.60 (1H, d, *J* = 7.5 Hz, OCHO), 4.59* (1H, d, *J* = 7.5 Hz, OCHO), 4.47* (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.43 (1H, dd, *J* = 7, 10 Hz, HC-5 Pro), 4.27 (1H, s, Pro-HC-2), 4.22* (1H, s, Pro-HC-2), 3.75 (3H, s, $H_3$CO=O), 3.74* (3H, s, $H_3$CO=O), 3.71 (, dd, *J* = 7, 10 Hz, Pro-HC-4), 3.67* (1H, dd, *J* = 7, 10 Hz, Pro-HC-4), 3.55 (1H, dd, *J* = 10, 10 Hz, Pro-HC-5), 3.28 (3H, s, $H_3$CO), 3.27* (3H, s, $H_3$CO), 3.08 (3H, s, Val$^1$-$H_3$CN), 2.88* (3H, s, Val$^1$-$H_3$CN), 2.85 (3H, s, Val$^2$-$H_3$CN), 2.84* (3H, s, Val$^2$-$H_3$CN), 2.40-2.12 (2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 1.58 (3H, s, $H_3$CC-3 ), 1.56* (3H, s, $H_3$CC-3 ), 1.02 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 1.01* (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 0.89 (9H, s, $(H_3C)_3$C), 0.88* (9H, s, $(H_3C)_3$C), 0.86 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.84 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.83* (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.79* (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.76 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 0.11 (3H, s, $H_3$CSi), 0.10* (3H, s, $H_3$CSi), 0.08 (3H, s, $H_3$CSi), 0.07* (3H, s, $H_3$CSi).

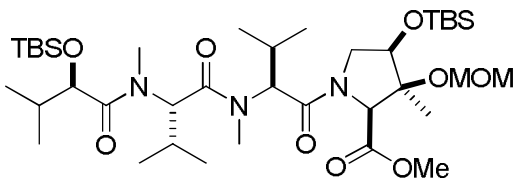
**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ 171.5 (s, Val$^2$-CO), 170.9* (s, Val$^1$-CO), 170.1* (s, Val$^1$-CO), 169.9 (s, Val$^1$-CO ), 167.56 (s, Pro-CO), 167.52* (s, Pro-CO), 157.1 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.9 (s, Ph), 128.8* (d ×2, Ph), 128.72* (d ×2, Ph), 128.69 (d ×2, Ph), 128.64* (d, Ph), 128.2 (d, Ph), 127.8 (d ×2, Ph), 92.8 (t, $CH_2O2$), 80.81 (s, Pro-C-3), 80.77* (s, Pro-C-3), 77.3 (d, Pro-C-4), 68.1* (d, $CH_2Ph$), 67.9 (d, Pro-C-2), 67.6 (t, $CH_2Ph$), 61.2* (d, Val$^1$-C-2), 60.8 (d, Val$^1$-C-2), 59.23* (d, Val$^1$-C-2), 59.19 (d, Val$^1$-C-2), 55.4 (q, $CH_3O$), 52.1 (q, $CH_3OC$=O), 50.27* (t, Pro-C-5), 50.27 (t, Pro-C-5), 30.7 (q, Val$^1$-$CH_3N$), 30.3* (q, Val$^1$-$CH_3N$), 29.9 (q, Val$^2$-$CH_3N$), 29.5* (q, Val$^2$-$CH_3N$), 28.13*

(d, $Val^1$-C-3), 28.07 (d, $Val^1$-C-3), 27.7* (d, $Val^1$-C-3), 27.6 (d, $Val^1$-C-3), 25.8 (q, $(CH_3)_3C$), 20.3* (q, $Val^1$-C-4), 20.1 (q, $Val^1$-C-4), 19.76* (q, $CH_3C$-3), 19.72 (q, $CH_3C$-3), 19.1 (q, $Val^1$-C-4), 19.0* (q, $Val^1$-C-4), 18.8* (q, $Val^1$-C-4), 18.6 (q, $Val^1$-C-4), 18.4* (q, $Val^2$-C-4), 18.3 (q, $Val^2$-C-4), 18.1 (s, $C(CH_3)_3$), -4.61 (q, $CH_3Si$), -5.01 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 694 ($[M+1]^+$, 66), 361 (100).

**HRMS** *m/z* calcd for $C_{35}H_{59}N_3O_9Si$ 693.4021 (694.4093 for M+H), found 694.4057 (ESI).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OMe (393a)**




**393a**

**Procedure:** Oxalyl chloride (0.013 mL, 0.018 g, 0.15 mmol) was added dropwise to a solution of Bis-TBS-acid **389** (0.034 g, 0.098 mmol) and DMF (ca. 1 μL, 0.01 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C under argon. After 0.5 h, the mixture was allowed to warm to ambient temperature. After 4 h, the mixture was diluted with dry hexane (5 mL) and the resulting solid was removed by filtration. The combined filtrate and hexane washings were concentrated to give the crude acid chloride. A stirred suspension of **392a** (0.022 g, 0.033 mmol) and 10 % Pd/C (9 mg) in $^i$PrOH (0.5 mL) was evacuated and $H_2$ gas was introduced using a balloon. After 4 h, the reaction mixture was passed through pad of Celite®. The combined filtrate and $CH_2Cl_2$ washings were concentrated to give the crude deprotected amine (0.018 g) that was dissolved in $CH_2Cl_2$ (1 mL) and the solution was added to the crude acid chloride. DIPEA (0.012 mL, 0.0085 g, 0.066 mmol) was added to the stirred mixture at 0 $^o$C. The mixture was allowed to warm to ambient temperature and after 4 h, was diluted with ethyl acetate, washed sequentially with water, 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated.

The resulting yellow oil was fractionated by FCC (30% ethyl acetate in hexane) to give **393a** as a colorless oil (0.022 g, 90%).

**$[\alpha]_D$** –96 (*c* 0.45, $CH_2Cl_2$)

**IR**: $\nu_{max}$: 1759, 1657, 1076$cm^{-1}$.

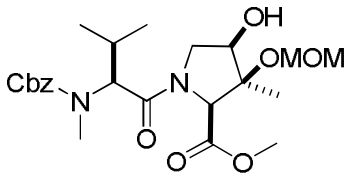
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.16 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 5.11 (1H, d, *J* = 11 Hz, $Val^2$-HC -2), 5.03 (1H, d, *J* = 11 Hz, $Val^1$-HC- 2), 4.62 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.46 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.28 (1H, s, Pro-HC-2), 4.11 (1H, d, *J* = 6.5 Hz, Hmb-HC -2), 3.76 (3H, s, $H_3COC$=O), 3.70 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-4), 3.54 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.29 (3H, s, $H_3CO$), 3.20 (3H, s, $H_3CN$), 3.15 (3H, s, $H_3CN$), 2.24-2.37 (2H, m, $Val^1$ & $Val^2$-HC -3), 1.93-2.00 (1H, m, Hmb-HC-3), 1.59 (3H, s, Pro $H_3CC$-3), 1.03 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.94 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.92 (9H, s, $(H_3C)_3C$), 0.91 (9H, s, $(H_3C)_3C$), 0.87-0.91 (6H, m, Hmb-$H_3C$-4 & $Val^2$-$H_3C$-4), 0.83 (3H, d, *J* = 6.5 Hz, $Val^2$-$H_3C$-4), 0.80 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.13 (3H, s, $H_3CSi$), 0.10 (3H, s, $H_3CSi$), 0.04 (3H, s, $H_3CSi$), 0.023 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.5 (s, $Val^3$-C- 1), 172.2 (s, $Val^2$-C- 1), 169.8 (s, $Val^1$-C- 1), 167.6 (s, Pro-CO), 92.8 (t, $OCH_2O$), 80.8 (s, Pro-C-3), 79.7 (d, $Val^3$-C- 2), 77.4 (d, Pro-C-4), 67.8 (d, Pro-C-2), 58.9 (d, $Val^1$-C- 2), 58.6 (d, $Val^2$-C- 2), 55.4 (q, $CH_3O$), 53.71 (t, Pro-C-5), 50.2 (t, Pro-C-5), 32.0 (d, $Val^3$-C- 3), 31.0 (q, $CH_3N$), 30.3 (q, $CH_3N$), 27.9 (d, $Val^1$-C- 3), 27.8 (d, $Val^2$-C- 3), 26.0 (q, $(CH_3)_3C$), 25.9 (q, $(CH_3)_3C$), 19.8 (q, Val-C-4), 19.7 (q, Pro $CH_3C$-3), 19.6 (q, Val-C-4), 19.1 (q, Val-C-4), 19.0 (q, Val-C-4), 18.7 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.2 (q, Val-C-4), 18.1 (s, $C(CH_3)_3$),-4.4 (q, $CH_3Si$),-4.6 (q, $CH_3Si$),-5.0 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity): 773 ($[M]^+$, 1), 716 (60), 441 (27), 328 (100), 187 (62), 86 (37), 73 (32).

**HRMS** *m/z* calcd for $C_{38}H_{75}N_3O_9Si_2$ 773.5042, found 773.5028.

**Cbz-MeVal-(4-OH)(3-OMOM)(3-Me)Pro-OMe (394)**




**394**

**Procedure:** TBAF (0.16 g, 0.60 mmol) was added to a stirred solution of **391a** (0.070 g, 0.12 mmol) in $CH_2Cl_2$ (1.2 mL) at room temperature. After 8 h, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated using FCC (50% ethyl acetate in hexane) to afford compound **394** (0.053 g, 94%) as a colorless oil.

**$[\alpha]_D$** −54 (*c* 1.55, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3436, 1762, 1690, 1642, 1020, 740 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.4:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.27-7.40 (5H, m, Ph), 5.29* (d, *J* = 11.6 Hz), 5.14 (s), 5.04* (2H, d, *J* = 11.6 Hz, $H_2CPh$), 4.81 (d, *J* = 7.2 Hz), 4.75* (1H, d, *J* = 7.2 Hz, $OCH_2O$), 4.72 (d, *J* = 7.2 Hz), 4.69* (1H, d, *J* = 7.2 Hz, $OCH_2O$), 4.57 (d, *J* = 11 Hz), 4.34* (1H, d, *J* = 11 Hz, Val-C-2), 4.31 (s), 4.22* (1H, s, Pro-HC-2), 4.14 (1H, dd, *J* = 5.5, 11 Hz, Pro-HC-5), 4.05 (d, *J* = 10.5 Hz), 3.98* (1H, d, *J* = 10.5 Hz, HO), 3.88 (ddd, *J* = 5.5, 5.5, 10.5 Hz), 3.58* (1H, ddd, *J* = 5.5, 5.5, 10.5 Hz, Pro-HC-4), 3.73 (s), 3.79* (3H, s, $H_3COC$=O), 3.39 (s), 3.37* (3H, s, $H_3CO$), 2.94 (s), 2.91* (3H, s, $H_3CN$), 2,19-2.28 (1H, m, Val-C-3), 1.45 (s), 1.31* (3H, s, Pro $H_3CC$-3), 1.00 (d, *J* = 6.5 Hz), 0.93* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.89 (d, *J* = 6.5 Hz), 0.85* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4).

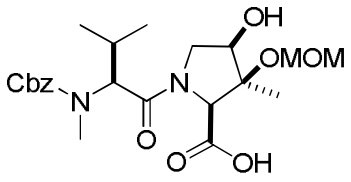
**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.4:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 171.1 (s, Pro-CO), 171.0* (s, Pro-CO), 170.7 (s, Val-C-1),

170.3* (s, Val-C-1), 157.4 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.8 (s, Ph), 136.4* (s, Ph), 129.0* (d, Ph), 128.84* (d, Ph), 128.77 (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 92.7* (t, $OCH_2O$), 92.6 (t, $OCH_2O$), 82.4 (s, Pro-C-3), 82.1* (s, Pro-C-3), 75.7 (d, Pro-C-4), 75.6* (d, Pro-C-4), 68.02* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 67.98* (d, Pro-C-2), 67.9 (d, Pro-C-2), 61.3* (d, Val-C-2), 61.1 (d, Val-C-2), 56.23 (q, $CH_3O$), 56.22* (q, $CH_3O$), 53.6 (t, Pro-C-5), 53.4* (t, Pro-C-5), 52.8* (q, $CH_3OC=O$), 52.7 (q, $CH_3OC=O$), 30.0* (q, $CH_3N$), 29.7 (q, $CH_3N$), 28.02* (d, Val-C-3), 27.97 (d, Val-C-3), 22.3* (q, Pro $CH_3C$-3), 22.0 (q, Pro $CH_3C$-3), 19.2* (q, Val-C-4), 19.04 (q, Val-C-4), 19.08* (q, Val-C-4), 19.03 (q, Val-C-4).

**LRMS** (EI), *m/z* (relative intensity):466 ($[M]^+$, .2), 248 (8), 220 (42), 176 (44), 91 (100), 70 (2).

**HRMS** *m/z* calcd for $C_{23}H_{34}N_2O_8$ 466.2315, found 466.2306.

**Cbz-MeVal-(4-OH)(3-OMOM)(3-Me)Pro-OH (395)**




**395**

**Procedure:** Trimethyltin hydroxide (0.19 g, 1.1 mmol) was added to a solution of carboxylic ester **394** (0.050 g, 0.11 mmol) in $(CH_2Cl)_2$ (1.5 mL) and the reaction mixture was heated in an oil bath at 80 $^oC$. After 2 d, the mixture was diluted with ethyl acetate and washed with 5% HCl (aq) and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to give **395** (0.041 g, 85%) as a thick colorless oil.

**$[\alpha]_D$** −104 (*c* 1.10, $CH_3OH$)

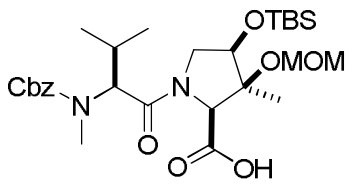
**IR**: $\nu_{max}$ 3373, 3142, 1689, 1652, 1029 $cm^{-1}$.

**$^{1}$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.7:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.41 (5H, m, Ph), 5.28* (d, *J* = 11.8 Hz), 5.15 (d, *J* = 12.6 Hz), 5.12 (d, *J* = 12.6 Hz), 5.06* (2H, d, *J* = 11.8 Hz, $H_2CPh$), 4.84 (d, *J* = 7.3 Hz), 4.80* (1H, d, *J* = 7.3 Hz, $OCH_2O$), 4.75 (d, *J* = 7.3 Hz), 4.69* (1H, d, *J* = 7.3 Hz, $OCH_2O$), 4.56 (d, *J* = 11.2 Hz), 4.32* (1H, d, *J* = 11.2 Hz, Val-C-2), 4.35 (s), 4.27* (1H, s, Pro-HC-2), 4.17 (dd, *J* = 5.5, 11 Hz), 3.54* (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 3.92 (dd, *J* = 5.5, 5.5 Hz), 3.60* (1H, dd, *J* = 5, 5 Hz, Pro-HC-4), 3.73 (dd, *J* = 5.5, 11 Hz), 3.50* (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 3.40 (s), 3.38* (3H, s, $H_3CO$), 2.93 (s), 2.91* (3H, s, $H_3CN$), 2.15-2.37 (1H, m, Val-HC-3), 1.49 (s), 1.35* (3H, s, Pro $H_3CC$-3), 0.98 (d, *J* = 6.5 Hz), 0.92* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.88 (d, *J* = 6.5 Hz), 0.85* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.7:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 172.4* (s, Pro-CO), 172.1 (s, Pro-CO), 171.2 (s, Val-C-1), 170.4* (s, Val-C-1), 157.5 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.6 (s, Ph), 136.3* (s, Ph), 128.9* (d, Ph), 128.8* (d, Ph), 128.7 (d, Ph), 128.3 (d, Ph), 127.9 (d, Ph), 92.5 (t, $OCH_2O$), 82.5 (s, Pro-C-3), 82.4* (s, Pro-C-3), 75.6 (d, Pro-C-4), 75.5* (d, Pro-C-4), 68.1* (t, $CH_2Ph$), 67.8 (t, $CH_2Ph$), 67.94 (d, Pro-C-2), 67.89* (d, Pro-C-2), 61.5* (d, Val-C-2), 61.2 (d, Val-C-2), 56.2* (q, $CH_3O$), 56.1 (q, $CH_3O$), 52.9 (t, Pro-C-5), 52.8* (t, Pro-C-5), 30.0* (q, $CH_3N$), 29.7 (q, $CH_3N$), 27.9 (d, Val-C-3), 21.6* (q, Pro $CH_3C$-3), 21.3 (q, Pro $CH_3C$-3), 19.2* (q, Val-C-4), 19.02 (q, Val-C-4), 19.00 (q, Val-C-4).

**HRMS** *m/z* calcd for $C_{22}H_{32}N_2O_8$ 452.2159 (451.2086 for M-H), found 451.2080 (ESI).

**Cbz-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OH (396)**




**396**

**Procedure:** 2,6-Lutidine (0.069 mL, 0.066 g, 0.62 mmol) and TBSOTf (0.10 mL, 0.12 g, 0.44 mmol) were sequentially added to a stirred solution of **395** (0.040 g, 0.088 mmol) in dry $CH_2Cl_2$ (1.5 mL) at 0 °C under Ar. After 15 min, the mixture was diluted with EtOAc and washed sequentially with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$ and concentrated to get crude tris-TBS derivative. A solution of aqueous LiOH (1 M; 0.45 mL, 0.45 mmol) was added to a solution of the above crude tris-TBS derivative in THF (1 mL) at 0 $^oC$. The reaction mixture was allowed to warm to room temperature and after 3 h, was diluted with $CH_2Cl_2$ and washed with 10% HCl. The organic layer was dried over $Na_2SO_4$, concentrated and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to afford compound **396** (0.042 g, 85%) as a thick colourless oil.

**$[\alpha]_D$** = -107 (*c* 0.40, $CH_3OH$)

**IR**: $\nu_{max}$ 3164, 1689, 1657, 1027 $cm^{-1}$.

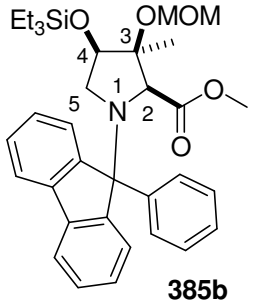
**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 5.8:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.39 (5H, m, Ph), 5.29* (d, *J* = 12.5 Hz, $H_2CPh$), 5.09-5.16 (m, $H_2CPh$ & $OCH_2O$), 5.07 (3H, d, *J* = 12.5 Hz, $H_2CPh$), 4.67 (d, *J* = 7.5 Hz), 4.65* (1H, d, *J* = 7.5 Hz, $H_2CPh$), 4.53 (d, *J* = 11 Hz), 4.34* (1H, d, *J* = 11 Hz, Val-HC-2), 4.35 (dd, *J* = 4, 10 Hz), 3.98* (1H, dd, *J* = 4, 6 Hz, Pro-HC-5), 4.30 (s), 4.29* (1H, s, Pro-HC-2), 3.80 (1H, dd, *J* = 6, 9 Hz, Pro-HC-4), 3.74* (dd, *J* = 6, 6 Hz), 3.54 (1H, dd, *J* = 9, 9 Hz, Pro-HC-5), 3.32 (s), 3.31* (3H, s, $H_3CO$), 2.93 (s), 2.92* (3H, s, $H_3CN$), 2.20-2.35 (1H, m, Val-HC-3), 1.59 (s), 1.53* (1H, s, Pro $H_3CC$-3), 0.99 (d, *J* = 6.5 Hz), 0.94* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.90 (s), 0.84* (9H, s, $(H_3C)_3C$), 0.88 (d, *J* = 6.5 Hz),

0.81* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.11 (s), 0.043* (3H, s, $H_3CSi$), 0.098 (s), 0.038* (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 5.8:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 170.55 (s, Pro-CO), 170.49 (s, Val-C-1), 169.4* (s, Val-C-1), 157.3 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.9 (s, Ph), 136.4* (s, Ph), 128.9* (d, Ph), 128.7 (d, Ph), 128.5* (d, Ph), 128.2 (d, Ph), 127.90 (d, Ph), 127.88* (d, Ph), 92.9 (t, $OCH_2O$), 81.0 (s, Pro-C-3), 80.9 (s, Pro-C-3), 77.3 (d, Pro-C-4), 67.8* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 67.7 (d, Pro-C-2), 62.0* (d, Val-C-2), 61.5 (d, Val-C-2), 55.7* (q, $CH_3O$), 55.6 (q, $CH_3O$), 50.6 (t, Pro-C-5), 30.1* (q, $CH_3N$), 29.7 (q, $CH_3N$), 28.0* (d, Val-C-3), 27.9 (d, Val-C-3), 25.8 (q, $(CH_3)_3C$), 25.7* (q, $(CH_3)_3C$), 19.97* (q, Pro $CH_3C$-3), 19.92 (q, Pro $CH_3C$-3), 19.4* (q, Val-C-4), 19.1 (q, Val-C-4), 18.92 (q, Val-C-4), 18.86* (q, Val-C-4), 18.1 (s, $C(CH_3)_3$), 18.0* (s, $C(CH_3)_3$),-4.66 (q, $CH_3Si$),-4.71* (q, $CH_3Si$), -4.8* (q, $CH_3Si$), -4.9 (q, $CH_3Si$).

**HRMS** *m/z* calcd for $C_{28}H_{46}N_2O_8Si$ 566.3023 (567.3096 for M+H), found 567.3137 (ESI).

**(2S,3S,4R)-methyl-3-(methoxymethoxy)-3-methyl-1-(9-phenyl-9H-fluoren-9-yl)-4-(triethyls-ilyloxy)pyrrolidine-2-carboxylate (385b)**




**385b**

**Procedure:** 2,6-Lutidine (0.110 mL, 0.105 g, 0.980 mmol) and $Et_3SiOTf$ (0.17 mL, 0.194 g, 0.735 mmol) were sequentially added to a stirred solution of alcohol **172** (0.225 g, 0.489 mmol) in dry $CH_2Cl_2$ (5 mL) at 0 °C. After 15 min, the mixture was diluted with

ethyl acetate and washed sequentially with sat. $NaHCO_3$, 5% aq. HCl, sat. $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (20 % ethyl acetate in hexane) to afford the title compound **385b** (0.260 g, 93%) as a white foam.

**$[\alpha]_D$** +202 (*c* 1.20, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3060, 1755, 1032, 739 $cm^{-1}$.

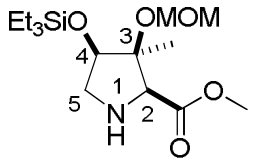
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.76 (1H, d, *J* = 7.5 Hz, Ar), 7.75-7.65 (3H, m, Ar), 7.45-7.51 (2H, m, Ar), 7.18-7.37 (6H, m, Ar), 7.07 (1H, dd, *J* = 7.5, 7.5 Hz, Ar), 5.13 (1H, d, *J* = 7.5 Hz, $HCO_2$), 4.56 (1H, d, *J* = 7.5 Hz, $HCO_2$), 3.47-3.57 (2H, m, HC-4 & 5), 3.44 (3H, s, $H_3COC$=O), 3.28 (1H, dd, *J* = 6, 10 Hz, HC-5), 3.21 (3H, s, $H_3CO$), 2.78 (1H, s, HC-2), 1.56 (3H, s, $H_3CC$-3), 0.90 (9H, dd, *J* = 8, 8 Hz, $H_2CSi$ ×3), 0.52 (6H, ddd, *J* = 8, 8, 8 Hz, $H_3CCSi$ ×3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 172.2 (s, $COOCH_3$), 147.6, 146.5, 143.6, 142.6, 139.2, 129.2, 128.58, 128.55, 128.4, 128.1, 127.7, 127.5, 127.1, 125.5, 120.3, 119.8, 92.5 (t, $OCH_2O$), 83.1 (s, C-3), 77.9 (s, Pf), 77.4 (d, C-4), 70.7 (d, C-2), 55.0 (q, $CH_3$-O), 54.5 (t, C-5), 51.3 (q, $CH_3OC$=O), 19.9 (q, $CH_3C$-3), 6.9 (q, $CH_3CSi$ ×3), 5.0 (t, $SiCH_2$).

**LRMS** (EI), *m/z* (relative intensity):573 ($[M]^+$, 1), 514 (13), 242 (22), 241 (100), 115 (1), 87 (1), 59 (1).

**HRMS** *m/z* calcd for $C_{34}H_{43}NO_5Si$ 573.2911, found 573.2906.

**Methyl (2S,3S,4R)-3-(Methoxymethoxy)-3-methyl-4-(triethylsilyloxy)pyrrolidine-2-carboxylate [(4-OTES)(3-OMOM)(3-Me)Pro-OMe] (388b)**




**388b**

**Procedure:** Using the same procedure as described for the preparation of **388a**, hydrogenolysis of **385b** (0.26 g, 0.45 mmol) gave **388b** (0.13 g, 88%) after fractionation of the crude by FCC (5% MeOH in $CH_2Cl_2$) as a pale yellow oil.

**$[\alpha]_D$** −54 (*c* 1.12, $CH_3OH$)

**IR** $\nu_{max}$ 1738 $cm^{-1}$.

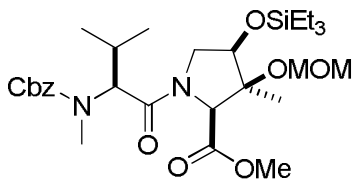
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.17 (1H, d, *J* = 7.5 Hz, $H_2CO$), 4.59 (1H, d, *J* = 7.5 Hz, $H_2CO$), 3.99 (1H, dd, *J* = 7.5, 9.5 Hz, HC-4), 3.78 (3H, s, $H_3COC$=O), 3.60 (1H, s, HC-2), 3.26 (3H, s, $H_3CO$), 3.10-2.99 (2H, m, $H_2C$-5), 2.51 (1H, br s, HN), 1.55 (3H, s, $H_3CC$-3), 0.94 (9H, t, *J* = 8 Hz, $H_3CCSi$ ×3), 0.58 (6H, ap q, *J* = 8, 8, 8 Hz, $H_2CSi$ ×3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 171.9 (s, C=O), 92.6 (t, $CH_2O2$), 82.3 (s, C-3), 79.5 (d, C-4), 68.6 (d, C-2), 55.2 (q, $CH_3O$), 52.2 (q, $CH_3OC$=O), 50.3 (t, C-5), 18.8 (q, $CH_3C$-3), 6.9 (q ×3, $CH_3CSi$), 4.9 (t ×3, $CH_2Si$).

**LRMS** (EI), *m/z* (relative intensity): 333 ($[M]^+$, 3), 288 (100), 244 (11), 188 (11), 156 (47), 115 (22), 87 (33).

**HRMS** *m/z* calcd for $C_{15}H_{31}NO_5Si$ 333.1971, found 333.1974 (EI).

**Cbz-MeVal-(4-OSiEt$_3$)(3-OMOM)(3-Me)Pro-OMe (391b)**




**391b**

**Procedure:** Using the same procedure as described for the preparation of **391a**, PyBroP (0.27 g, 0.58 mmol), DIPEA (0.14 mL, 0.10 g, 0.78 mmol) mediated coupling of **388b** (0.13 g, 0.39 mmol) with Cbz-MeVal-OH (**60**) (0.13 g, 0.51 mmol) gave **391b** (0.020 g, 90%) after fractionation of the crude by FCC (30% EtOAc in Hexane) as a white solid.

**[α]$_D$** −92 (*c* 1.46, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1762, 1690, 1648, 1026, 745 cm$^{-1}$.

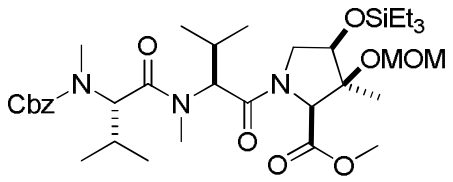
**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 5.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.39 (5H, m, Ph), 5.37* (d, *J* = 13 Hz), 5.14 (d, *J* = 12.8 Hz), 5.10 (d, *J* = 12.8 Hz), 5.03* (2H, d, *J* = 13 Hz, $H_2$CPh), 5.17 (d, *J* = 7.5 Hz), 5.11* (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.60 (d, *J* = 7.5 Hz), 4.58* (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.54 (1H, d, *J* = 11 Hz, Val-HC-2), 4.38 (1H, dd, *J* = 7. 9.5 Hz, Pro-HC-5), 4.26 (1H, s, Pro-HC-2), 3.78 (1H, dd, *J* = 7, 9.5 Hz, Pro-HC-4), 3.75 (3H, s, $H_3$COC=O), 3.52 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.28 (s), 3.27* (3H, s, $H_3$CO), 2.94 (s), 2.93* (3H, s, $H_3$CN), 2.20-2.34 (1H, m, Val-HC-3), 1.60 (s), 1.57* (3H, s, Pro $H_3$CC-3), 1.03 (d, *J* = 6.5 Hz), 1.00* (3H, d, *J* = 6.5 Hz, Val-$H_3$C-4), 0.96 (dd, *J* = 8, 8 Hz), 0.89* (9H, m, $H_3$CCSi ×3), 0.88 (d, *J* = 6.5 Hz), 0.80* (3H, d, *J* = 6.5 Hz, Val-$H_3$C-4), 0.62 (ddd, *J* = 8, 8, 8 Hz), 0.46-0.56 (6H, m, $H_2$CSi ×3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 5.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 170.2 (s, Pro-CO), 169.2* (s, Pro-CO), 167.6 (s, Val-C-1),

167.4* (s, Val-C-1), 157.2 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.9 (s, Ph), 136.5* (s, Ph), 128.8* (d, Ph), 128.7 (d, Ph), 128.3* (d, Ph), 128.2 (d, Ph), 128.0 (d, Ph), 127.5* (d, Ph), 92.7 (t, $OCH_2O$), 80.7 (s, Pro-C-3), 80.6* (s, Pro-C-3), 77.0 (d, Pro-C-4), 76.9* (d, Pro-C-4), 67.9 (d, Pro-C-2), 66.3* (d, Pro-C-2), 67.6* (t, $CH_2Ph$), 67.5 (t, $CH_2Ph$), 62.0* (d, Val-C-2), 61.5 (d, Val-C-2), 55.34* (q, $CH_3O$), 55.29 (q, $CH_3O$), 52.1* (q, $CH_3OC=O$), 52.0 (q, $CH_3OC=O$), 50.1 (t, Pro-C-5), 30.1* (q, $CH_3N$), 29.6 (q, $CH_3N$), 28.1* (d, Val-C-3), 28.0 (d, Val-C-3), 19.60 (q, Pro $CH_3C$-3), 19.57* (q, Pro $CH_3C$-3), 19.3* (q, Val-C-4), 19.1 (q, Val-C-4), 18.9 (q, Val-C-4), 18.8* (q, Val-C-4), 6.9 (q, $CH_3CSi \times 3$), 6.8* (q, $CH_3CSi \times 3$), 4.78* (t, $CH_2Si \times 3$), 4.76 (t, $CH_2Si \times 3$).

**HRMS** *m/z* calcd for $C_{29}H_{48}N_2O_8Si$ 580.3180 (581.3253 for M+H), found 581.3259 (ESI).

**Cbz-MeVal-MeVal-(4-OSiEt$_3$)(3-OMOM)(3-Me)Pro-OMe (392b)**




**392b**

**Procedure:** Using the same procedure as described for the preparation of **392a**, hydrogenolysis of **391b** (0.070 g, 0.12 mmol) followed by PyBroP (0.84 g, 0.18 mmol), DIPEA (0.042 mL, 0.031 g, 0.24 mmol) mediated coupling with Cbz-MeVal-OH (0.041 g, 1.6 mmol) gave **392b** (0.071 g, 85%) after fractionation of the crude by FCC (30% EtOAc in hexane) thick colorless oil.

**[α]$_D$** −112 (*c* 1.4, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1762, 1731, 1696, 1642, 1020, 745 $cm^{-1}$.

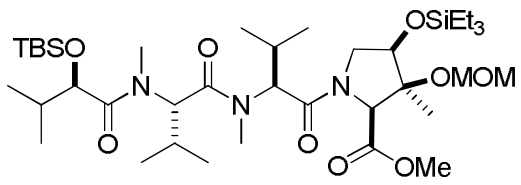
**$^{1}$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.38 (5H, m, Ph), 5.23* (d, *J* = 12 Hz), 5.17-5.20 (m), 5.09* (3H, d, *J* = 12 Hz, $H_2CPh$ & $OCH_2O$), 5.00 (d, *J* = 11 Hz), 4.96* (1H, d, *J* = 11 Hz, $Val^2$-HC -2), 4.73 (d, *J* = 11 Hz), 4.48* (1H, d, *J* = 11 Hz, Val 1 CH-2), 4.61 (d, *J* = 7.5 Hz), 4.60* (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.42 (1H, dd, *J* = 7, 9.5 Hz, Pro-HC-5), 4.27 (s), 4.22* (1H, s, Pro-HC-2), 3.76 (s), 3.75* (3H, s, $H_3COC$=O), 3.67-3.74 (2H, m, Pro-HC-4 & 5), 3.54 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.28 (s), 3.27* (3H, s, $H_3CO$), 3.09 (s), 2.89* (3H, s, $H_3CN$), 2.87 (s), 2.85* (3H, s, $H_3CN$), 2.13-2.40 (2H, m, Val 1, $Val^2$-HC -3), 1.60 (s), 1.58 (3H, s, Pro $H_3CC$-3), 1.03 (d, *J* = 7 Hz), 1.02* (3H, d, *J* = 7 Hz, $Val^1$-$H_3C$-4), 0.93-0.99 (9H, m, $H_3CCSi$ ×3), 0.88 (d, *J* = 7 Hz), 0.84* (3H, d, *J* = 7 Hz, $Val^1$-$H_3C$-4), 0.86 (d, *J* = 7 Hz), 0.81* (3H, d, *J* = 7 Hz, Val 2 HC-4), 0.77 (d, *J* = 7 Hz), 0.76* (3H, d, *J* = 7 Hz, $Val^2$-$H_3C$-4), 0.58-0.66 (6H, m, $H_2CSi$ ×3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 171.4 (s, $Val^1$-C- 1), 170.9* (s, $Val^1$-C- 1), 170.0* (s, $Val^2$-C- 1), 169.8 (s, $Val^2$-C- 1), 167.63* (s, Pro-CO), 167.56 (s, Pro-CO), 157.1 (s, $NCO_2$), 156.2 (s, $NCO_2$), 136.9 (s, Ph), 136.5* (s, Ph), 128.8* (d, Ph), 128.72* (d, Ph), 128.69 (d, Ph), 128.6* (d, Ph), 128.2 (d, Ph), 127.8 (d, Ph), 92.7 (t, $OCH_2O$), 80.75 (s, Pro-C-3), 70.71* (s, Pro-C-3), 77.1 (d, Pro-C-4), 68.1* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 67.9 (d, Pro-C-2), 61.2* (d, $Val^2$-C- 2), 60.7 (d, $Val^2$-C- 2), 59.20* (d, $Val^1$-C- 2), 59.18 (d, $Val^1$-C- 2), 55.3 (q, $CH_3O$), 52.0 (q, $CH_3OC$=O), 50.3 (t, Pro-C-5), 30.7 (q, $CH_3N$), 30.3* (q, $CH_3N$), 29.9* (q, $CH_3N$), 29.5 (q, $CH_3N$), 28.14* (d, $Val^1$-C- 3), 28.07 (d, $Val^1$-C- 3), 27.8* (d, $Val^2$-C- 3), 27.6 (d, $Val^2$-C- 3), 20.1* (q, Val-C-4), 19.9 (q, Val-C-4), 19.73* (q, Pro $CH_3C$-3), 19.71 (q, Pro $CH_3C$-3), 19.1 (q, Val-C-4), 19.0* (q, Val-C-4), 18.8* (q, Val-C-4), 18.6 (q, Val-C-4), 18.4* (q, Val-C-4), 18.3 (q, Val-C-4), 6.9 (q, $CH_3CSi$ ×3), 4.8 (t, $CH_2Si$ ×3).

**LRMS** (EI), *m/z* (relative intensity):693 ($[M]^+$, 1.5), 473 (4), 361 (42), 248 (43), 176 (65), 91 (100), 86 (18).

**HRMS** *m/z* calcd for $C_{35}H_{59}N_3O_9Si$ 693.4021, found 693.4010.

**TBS-Hmb-MeVal-MeVal-(4-OSiEt$_3$)(3-OMOM)(3-Me)Pro-OMe (393b)**




**393b**

**Procedure:** Using the same procedure as described for the preparation of **393a**, hydrogenolysis of **392b** (0.051 g, 0.073 mmol) followed by DIPEA (0.019 mL, 0.014 g, 0.11 mmol) mediated coupling with the acid chloride prepared from **389** (0.037 g, 0.15 mmol) gave **393b** (0.048 g, 85%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick colourless oil.

**[α]$_D$** −95 (*c* 2.06, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1767, 1731, 1650, 1630 cm$^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.13 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 5.10 (1H, d, *J* = 11 Hz, Val$^2$-HC -2), 5.02 (1H, d, *J* = 11 Hz, Val$^1$-HC- 2), 4.60 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.43 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.26 (1H, s, Pro-HC-2), 4.10 (1H, d, *J* = 6.5 Hz, Hmb-HC -2), 3.75 (3H, s, $H_3COC$=O), 3.71 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 3.53 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.28 (3H, s, $H_3CO$), 3.19 (3H, s, $H_3CN$), 3.15 (3H, s, $H_3CN$), 2.22-2.37 (2H, m, Val$^1$ & Val$^2$-HC -3), 1.91-2.00 (1H, m, Hmb-HC -3), 1.60 (3H, s, Pro $H_3CC$-3), 1.02 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.97 (9H, dd, *J* = 7.5, 7.5 Hz, $H_3CCSi$ ×3), 0.87-0.95 (18H, m, $(H_3C)_3C$, Val-$H_3C$-4 & 2xHmb-$H_3C$-4), 0.83 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.79 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.63 (6H, ddd, *J* = 7.5, 7.5, 7.5 Hz, $H_2CSi$ ×3), 0.03 (3H, s, $H_3CSi$), 0.02 (3H, s, $H_3CSi$).

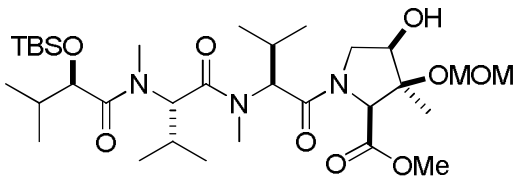
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.5 (s, Val$^3$-C- 1), 172.2 (s, Val$^2$-C- 1), 169.7 (s, Val$^1$-C- 1), 167.6 (s, Pro-CO), 92.7 (t, $OCH_2O$), 80.7 (s, Pro-C-3), 79.4 (d, Val$^3$-C- 2), 77.2 (d,

Pro-C-4), 67.8 (d, Pro-C-2), 58.9 (d, Val[1]-C- 2), 58.5 (d, Val[2]-C- 2), 55.3 (q, $CH_3O$), 52.0 (q, $CH_3OC{=}O$), 50.3 (t, Pro-C-5), 31.9 (d, Val[3]-C- 3), 30.9 (q, $CH_3N$), 30.2 (q, $CH_3N$), 27.9 (d, Val[1]-C- 3), 27.8 (d, Val[2]-C- 3), 26.0 (q, $(CH_3)_3C$), 19.8 (q, Val-C-4), 19.59 (q, Val-C-4), 19.57 (q, Val-C-4), 19.0 (q, Val-C-4), 18.7 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.2 (q, Val-C-4), 6.9 (t, $CH_3CSi \times 3$), 4.8 (t, $CH_2Si \times 3$),-4.4 (q, $CH_3Si$),-5.0 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):773 ($[M]^+$, 1), 716 (54), 441 (21), 328 (100), 300 (26), 187 (49), 86 (32), 73 (20).

**HRMS** *m/z* calcd for $C_{38}H_{75}N_3O_9Si_2$ 773.5042, found 773.5045.

**TBS-Hmb-MeVal-MeVal-(4-OH)(3-OMOM)(3-Me)Pro-OMe (397)**




**397**

**Procedure:** Pyridine (0.12 mL) and HF·pyridine (0.12 mL) were added to a stirred solution of **393b** (40 mg, 0.052 mmol) in THF (1 mL) at 0 °C. After 1 h, the mixture was quenched by addition of sat. $NaHCO_3$ (aq.) (caution $CO_2$ evolution), and then was diluted with ethyl acetate, washed sequentially with 2% aqueous citric acid (×3), sat. $NaHCO_3$ (aq.) and brine, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give **397** (32 mg, 95%) as a thick colorless oil.

**$[\alpha]_D$** −89 (*c* 1.1, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3424, 1762, 1720, 1624 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.11 (1H, d, *J* = 11 Hz, Val[2]-HC -2), 5.04 (1H, d, *J* = 11 Hz, Val[1]-HC- 2), 4.82 (1H, d, *J* = 7.3 Hz, $OCH_2O$), 4.74 (1H, d, *J* = 7.3 Hz, $OCH_2O$), 4.33 (1H, s, Pro-HC-2), 4.24 (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 4.12 (1H, d, *J* = 11 Hz,

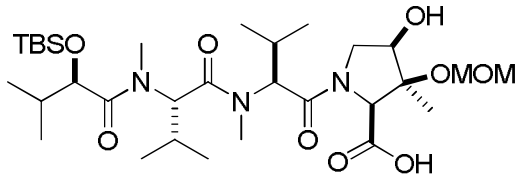
HO), 4.10 (1H, d, *J* = 6.5 Hz, Val$^3$-C- 2), 3.90 (1H, ddd, *J* = 5, 5, 11 Hz, Pro-HC-4), 3.81 (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 3.79 (3H, s, $H_3COC$=O), 3.42 (3H, s, $H_3CO$), 3.21 (3H, s, $H_3CN$), 3.14 (3H, s, $H_3CN$), 2.22-2.28 (2H, m, Val 1 & Val$^2$-HC -3), 1.90-2.01 (1H, m, Val 3 CH-3), 1.46 (3H, s, Pro $H_3CC$-3), 1.01 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.94 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.91 (9H, s, $(H_3C)_3C$), 0.89 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.88 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.82 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.81 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.040 (3H, s, $H_3CSi$), 0.026 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.6 (s, Val$^3$-C- 1), 172.5 (s, Val$^2$-C- 1), 170.9 (s, Pro-CO), 170.7 (s, Val$^1$-C- 1), 92.7 (t, $OCH_2O$), 82.3 (s, Pro-C-3), 79.8 (d, Val$^3$-C- 2), 75.7 (d, Pro-C-4), 67.8 (d, Pro-C-2), 58.6 (d, Val$^1$-C- 2), 58.5 (d, Val2 C-2), 56.2 (q, $CH_3O$), 53.9 (t, Pro-C-5), 52.7 (q, $CH_3OC$=O), 32.0 (d, Val$^3$-C- 3), 31.0 (q, $CH_3N$), 29.9 (q, $CH_3N$), 27.8 (d, Val$^2$-C- 3), 27.6 (d, Val$^1$-C- 3), 26.0 (q, $(CH_3)_3C$), 22.0 (q, Pro $CH_3C$-3), 19.5 (q, Val-C-4), 19.3 (q, Val-C-4), 19.04 (q, Val-C-4), 19.00 (q, Val-C-4), 18.8 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.3 (q, Val-C-4),-4.4 (s, $CH_3Si$),-5.0 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):659 ([M]$^+$, 1), 602 (45), 441 (18), 328 (100), 300 (40), 187 (99.8), 86 (67), 73 (45).

**HRMS** *m/z* calcd for $C_{32}H_{61}N_3O_9Si$ 659.4177, found 659.4156.

**TBS-Hmb-MeVal-MeVal-(4-OH)(3-OMOM)(3-Me)Pro-OH (398)**




**398**

**Procedure:** Trimethyltin hydroxide (0.055 g, 0.30 mmol) was added to a solution of carboxylic ester **397** (0.020 g, 0.030 mmol) in $(CH_2Cl)_2$ (0.5 mL) and the reaction mixture was heated in an oil bath at 80 $^o$C. After 2 days, the mixture was diluted with

ethyl acetate and washed with 5% HCl (aq.) and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to give **398** (0.017 g, 87%) as a thick oil.

**$[\alpha]_D$** −111 (*c* 0.40, $CH_3OH$)

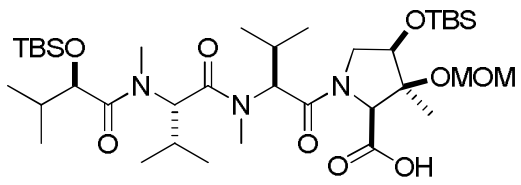
**IR**: $\nu_{max}$ 3406, 3148, 1754, 1722, 1635 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.10 (1H, d, *J* = 11 Hz, $Val^2$-HC -2), 5.02 (1H, d, *J* = 11 Hz, $Val^1$-HC- 2), 4.87 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.73 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.36 (1H, s, Pro-C-2), 4.22 (1H, dd, *J* = 4.5, 11 Hz, Pro-HC-5), 4.10 (1H, d, *J* = 6.5 Hz, $Val^3$-C- 2), 3.92 (1H, dd, *J* = 4.5, 4.5 Hz, Pro-HC-4), 3.80 (1H, dd, *J* = 4.5, 11 Hz, Pro-HC-5), 3.43 (3H, s, $H_3CO$), 3.20 (3H, s, $H_3CN$), 3.13 (3H, s, $H_3CN$), 2.24-2.36 (2H, m, $Val^1$, $Val^2$ HC-3), 1.90-1.99 (1H, m, $Val^3$-HC -3), 1.46 (3H, s, Pro $H_3CC$-3), 0.98 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.93 (3H, s, *J* = 6.5 Hz, Val-$H_3C$-4), 0.90 (9H, s, $(H_3C)_3C$), 0.85-0.89 (6H, m, Val-$H_3C$-4 & Val-$H_3C$-4), 0.82 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.79 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.033 (3H, s, $H_3CSi$), 0.018 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.6 (s, $Val^3$-C- 1), 172.5 (s, $Val^2$-C- 1), 171.3 (s, Pro-CO), 170.6 (s, $Val^1$-C- 1), 92.5 (t, $OCH_2O$), 82.7 (s, Pro-C-3), 79.8 (d, $Val^3$-C- 2), 75.7 (d, Pro-C-4), 67.9 (d, Pro-C-2), 58.70 (d, $Val^1$-C- 2), 58.67 (d, $Val^2$-C- 2), 58.3 (q, $CH_3O$), 53.2 (t, Pro-C-5), 32.0 (d, $Val^3$-C- 3), 31.1 (q, $CH_3N$), 30.2 (q, $CH_3N$), 27.7 (d, $Val^2$-C- 3), 27.6 (d, $Val^1$-C- 3), 26.0 (q, $(CH_3)_3C$), 21.5 (q, Pro $CH_3C$-3), 19.5 (q, Val-C-4), 19.3 (q, Val-C-4), 19.1 (q, Val-C-4), 19.0 (q, Val-C-4), 18.8 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.3 (q, Val-C-4),-4.4 (q, $CH_3Si$),-5.0 (q, $CH_3Si$).

**HRMS** *m/z* calcd for $C_{31}H_{59}N_3O_9Si$ 645.4021, (646.4093 for M+H), found 646.4086 (ESI).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OH (399)**




**399**

**Procedure:** 2,6-Lutidine (0.021 mL, 0.020 g, 0.18 mmol) and TBSOTf (0.030 mL, 0.035 g, 0.13 mmol) were sequentially added to a stirred solution of **398** (0.017 g, 0.026 mmol) in dry $CH_2Cl_2$ (0.5 mL) at 0 °C under Ar. After 15 min, the mixture was diluted with EtOAc and washed sequentially with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$ and concentrated to get crude tris-TBS derivative. A solution of aqueous LiOH (0.5 M; 0.70 mL, 0.35 mmol) was added to a solution of the above crude tris-TBS derivative in THF (1 mL) at 0 $^oC$. The reaction mixture was allowed to warm to room temperature and after 3 h, was diluted with $CH_2Cl_2$ and washed with 10% HCl. The organic layer was dried over $Na_2SO_4$, concentrated and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to afford compound **399** (0.017 g, 86%) as a thick oil.

**$[\alpha]_D$** −82 (*c* 0.53, $CH_3OH$)

**IR**: $\nu_{max}$ 3137, 1754, 1722, 1635 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.07-5.13 (2H, m, $OCH_2O$ & $Val^2$-HC -2), 5.00 (1H, d, *J* = 11 Hz, $Val^1$-HC- 2), 4.67 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.40 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.29 (1H, s, Pro-HC-2), 4.09 (1H, d, *J* = 6.5 Hz, $Val^3$-HC -2), 3.72 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-4), 3.56 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.32 (3H, s, $H_3CO$), 3.18 (3H, s, $H_3CN$), 3.13 (3H, s, $H_3CN$), 2.21-2.36 (2H, m, Val 1 & $Val^2$-HC -3), 1.90-1.99 (1H, m, $Val^3$-HC -3), 1.58 (3H, s, Pro $H_3CC$-3), 0.97 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.92 (3H, d, *J* = 6.5 Hz, $Val^3$-$H_3C$-4), 0.84-0.91 (24H, m, 2X$(H_3C)_3C$, $Val^2$-$H_3C$-4 &

$Val^3$-$H_3C$-4), 0.82 (3H, d, *J* = 6.5 Hz, $Val^2$-$H_3C$-4), 0.77 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.11 (3H, s, $H_3CSi$), 0.092 (3H, s, $H_3CSi$), 0.028 (3H, s, $H_3CSi$), 0.014 (3H, s, $H_3CSi$).

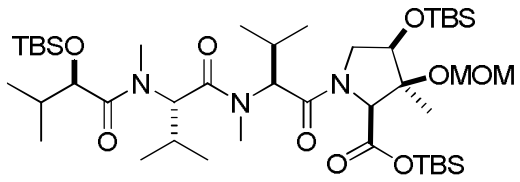
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.6 (s, $Val^3$-C- 1), 172.3 (s, $Val^2$-C- 1), 170.5 (s, Pro-CO), 170.0 (s, $Val^1$-C- 1), 92.9 (t, $OCH_2O$), 81.1 (s, Pro-C-3), 79.8 (d, $Val^3$-C- 2), 77.4 (d, Pro-C-4), 67.6 (d, Pro-C-2), 58.9 (d, $Val^1$-C- 2), 58.6 (d, $Val^2$-C- 2), 55.6 (q, $CH_3O$), 50.8 (t, Pro-C-5), 32.0 (d, $Val^3$-C- 3), 31.0 (q, $CH_3N$), 30.2 (q, $CH_3N$), 27.85 (d, $Val^2$-C-3), 27.75 (d, $Val^1$-C- 3), 26.0 (q, $(CH_3)_3C$), 25.8 (q, $(CH_3)_3C$), 20.1 (q, Pro $CH_3C$-3), 19.65 (q, $Val^3$-C- 4), 19.58 (q, $Val^2$-C- 4), 19.1 (q, $Val^2$-C- 4), 19.0 (q, $Val^1$-C- 4), 18.7 (q, $Val^1$-C- 4), 18.4 (s, $C(CH_3)_3$), 18.2 (q, $Val^3$-C- 4), 18.1 (s, $C(CH_3)_3$),-4.4 (q, $CH_3Si$),-4.7 (s, $CH_3Si$),-4.99 (q, $CH_3Si$),-5.02 (s, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 782 ($[M+23]^+$, 1), 760 ($[M+1]^+$, 100), 441 (2), 328 (1).

**HRMS** *m/z* calcd for $C_{37}H_{73}N_3O_9Si_2$ 759.4885 (760.4958 for M+H), found 760.4967 (ESI).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OTBS:**

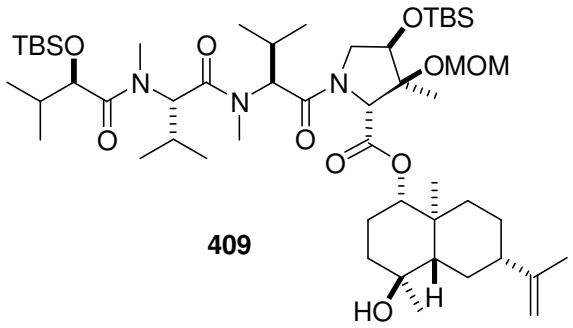
Intermediate tris TBS derivative showed the following $^1$H NMR:




**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.13 (1H, d, *J* = 7.5 Hz, OCHO), 5.10 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.07 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.66 (1H, d, *J* = 7.5 Hz, OCHO), 4.42 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.24 (1H, s, Pro-HC-2), 4.10 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.65 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-4), 3.53 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.32 (3H, s, $H_3CO$), 3.20 (3H, s, $Val^2$-$H_3CN$), 3.13 (3H, s, $Val^1$-$H_3CN$), 2.37-2.22

(2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 1.99-1.90 (1H, m, Hmb-HC-3), 1.60 (3H, s, Pro-$H_3$CC-3), 1.02 (3H, d, *J* = 6.5 Hz), 0.95 (9H, s, ($H_3$C)3C), 0.92 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz), 0.90 (9H, s, ($H_3$C)3C), 0.89 (9H, s, ($H_3$C)3C), 0.87 (3H, d, *J* = 6.5 Hz), 0.83 (3H, d, *J* = 6.5 Hz), 0.77 (3H, d, *J* = 6.5 Hz), 0.31 (3H, s, $H_3$CSi), 0.30 (3H, s, $H_3$CSi), 0.11 (3H, s, $H_3$CSi), 0.088 (3H, s, $H_3$CSi), 0.027 (3H, s, $H_3$CSi), 0.013 (3H, s, $H_3$CSi).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-Lar (409)**




**409**

**[α]$_D$** –96 (*c* 0.54, $CH_2Cl_2$)

**IR** (DRIFT) $\nu_{max}$ 3382, 1738, 1636 cm$^{-1}$.

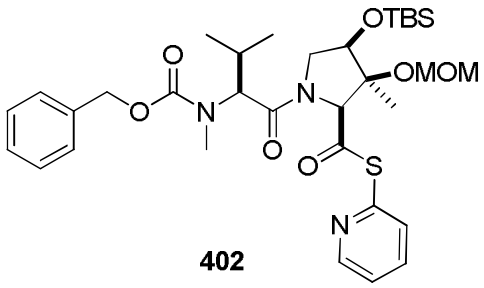
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.10 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 5.09 (1H, d, *J* = 7 Hz, $OCH_2O$), 5.02 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.72-4.68 (2H, m, Lar-$H_2$C-2), 4.65 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.59 (1H, dd, *J* = 4, 11.5 Hz, Lar-HC-1), 4.41 (1H, dd, *J* = 7, 9.5 Hz, Pro-HC-5), 4.19 (1H, s, Pro-HC-2), 4.10 (1H, d, *J* = 6 Hz, Hmb-HC-2), 3.69 (1H, dd, *J* = 7, 9.5 Hz, Pro-HC-4), 3.57 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.29 (3H, s, $H_3CO$), 3.20 (3H, s, Val$^1$-$H_3$CN), 3.13 (3H, s, Val$^2$-$H_3$CN), 2.40-2.18 (2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 2.10-1.53 (10H, m), 1.74 (3H, s, Lar-$H_3$C-13), 1.57 (3H, s, Pro-$H_3$CC-3), 1.40-1.16 (4H, m), 1.13 (3H, s, Lar-$H_3$C-14), 1.03 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 0.99 (3H, s, Lar-$H_3$C-15), 0.92 (3H, d, *J* = 6.5 Hz, Hmb-$H_3$C-4), 0.90 (9H, s, ($H_3$C)3C), 0.89 (9H, s, ($H_3$C)3C), 0.88 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4 or Hmb-$H_3$C-4), 0.87 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4 or Hmb-$H_3$C-4), 0.82 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.78 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 0.11 (3H, s, $H_3$CSi), 0.085 (3H, s, $H_3$CSi), 0.029 (3H, s, $H_3$CSi), 0.013 (3H, s, $H_3$CSi).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.5 (s, Hmb-CO), 172.1 (s, $Val^2$-CO), 169.8 (s, $Val^1$-CO), 166.3 (s, Pro-CO), 150.5 (s, Lar-C-11), 108.6 (t, Lar-C-12), 92.8 (t, $OCH_2O$), 82.5 (d, Lar-C-1), 80.7 (s, Pro-C-3), 79.6 (d, Hmb-C-2), 77.2 (d, Pro-C-4), 71.6 (s, Lar-C-4), 68.1 (d, Pro-C-2), 59.0 (d, $Val^1$-C-2), 58.6 (d, $Val^2$-C-2), 56.2 (q, $CH_3O$), 53.5 (d, Lar-C-5), 50.5 (t, Pro-C-5), 45.8 (d, Lar-C-7), 40.88 (t, Lar-C-3 or C-9), 40.83 (t, Lar-C-9 or C-3), 38.3 (s, Lar-C-10), 32.0 (d, Hmb-C-3), 31.1 (q, $Val^1$-$CH_3N$), 30.2 (q, $Val^2$-$CH_3N$), 27.8 (d, $Val^1$-C-3), 27.8 (d, $Val^2$-C-3), 26.5 (t, Lar-C-8), 26.0 (q, $(CH_3)_3C$), 25.93 (t, Lar-C-6), 25.86 (q, $(CH_3)_3C$), 25.3 (t, Lar-C-2), 22.9 (q, Lar-C-14), 21.3 (q, Lar-C-13), 19.7 (q, $Val^2$-C-4), 19.6 (q, Pro-$CH_3$C-3), 19.6 (s, $C(CH_3)3$), 19.3 (q, $Val^2$-C-4 or C-4 Hmb), 19.0 (q, $Val^1$-C-4), 18.7 (q, $Val^2$-C-4 or C-4 Hmb), 18.4 (q, $Val^1$-C-4), 18.1 (q, Hmb-C-4), 18.1 (s, $C(CH_3)3$), 14.5 (q, Lar-C-15), -4.4 (q, $CH_3Si$), -4.6 (q, $CH_3Si$), -5.01 (q, $CH_3Si$), -5.06 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 1002 ($[M+23]^+$, 85), 980 ($[M+1]^+$, 75), 706 (70), 549 (88), 433 (80), 413 (72), 391 (100), 248 (73), 130 (90).

**HRMS** *m/z* calcd. for $C_{52}H_{97}N_3O_{10}Si_2$: 979.6712 (980.6785 for M+H); found: 980.6761 (ESI).

**Cbz-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-SPy (402)**




**402**

**Procedure:** $PPh_3$ (0.029 g, 0.11 mmol) and $(2\text{-PyS})_2$ (0.023 g, 0.11 mmol) were sequentially added to a stirred solution of **396** (0.040 g, 0.071 mmol) in THF (0.7 mL) at room temperature under argon. After 16 h the reaction mixture was concentrated and fractionated by PTLC (50% ethyl acetate in hexane to afford **402** (0.037 g, 80%) as a pale yellow oil.

**$[\alpha]_D$** = -124 (*c* 1.20, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1693, 1656, 1023, 776 $cm^{-1}$.

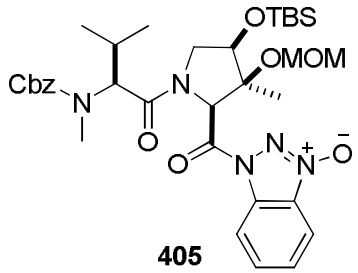
**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 6.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 8.53 (1H, ddd, *J* = 1, 2, 5 Hz, Py), 7.75 (1H, ddd, *J* = 1, 1, 8 Hz, Py), 7.69 (1H, ddd, *J* = 2, 8, 8 Hz, Py), 7.27-7.39 (5H, m, Ph), 7.22 (1H, ddd, *J* = 1, 5, 8 Hz, Py), 4.95-5.37 (3H, m, $H_2CPh$ & $OCH_2O$), 4.64 (1H, d, *J* = 7.5 Hz, $OCH_2O$), 4.59 (d), 4.41* (1H, d, *J* = 11 Hz, Val-C-2), 4.47* (s), 4.46 (1H, s, Pro-HC-2), 4.44 (dd), 3.87* (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 3.74 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-4), 3.60 (dd), 3.54* (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.34* (s), 3.21 (3H, s, $H_3CO$), 2.94 (s), 2.91* (3H, s, $H_3CN$), 2.15-2.40 (1H, m, Val-C-3), 1.66 (s), 1.62* (3H, s, Pro $H_3CC$-3), 1.05 (d), 1.00* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.86-0.92 (m), 0.85* (s), 0.79* (12H, d, *J* = 6.5 Hz, $(H_3C)_3C$ & Val-$H_3C$-4), 0.12 (s), 0.044* (3H, s, $H_3CSi$), 0.089 (s),-0.023* (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 6.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 191.8 (s, Pro-CO), 191.6* (s, Pro-CO), 170.7 (s, Val-C-1), 169.5* (s, Val-C-1), 157.2 (s, $NCO_2$), 156.1* (s, $NCO_2$), 152.3 (s, Py), 152.2* (s, Py), 150.2 (d, Py), 137.00* (d, Py), 136.96 (d, Py), 136.8 (s, Ph), 136.3* (s, Ph), 129.93 (d, Py), 129.90* (d, Py), 128.9* (d, Ph), 128.71 (d, Ph), 128.67* (d, Ph), 128.2 (d, Ph), 127.91* (d, Ph), 127.87 (d, Ph), 123.35* (d, Py), 123.31 (d, Py), 92.9* (t, $OCH_2O$), 92.8 (t, $OCH_2O$), 81.3 (s, Pro-C-3), 81.2* (s, Pro-C-3), 77.3 (d, Pro-C-4), 74.0 (d, Pro-C-2), 73.7* (d, Pro-C-2), 67.9* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 62.4* (d, Val-C-2), 61.7 (d, Val-C-2), 55.8* (q, $CH_3O$), 55.7 (q, $CH_3O$), 50.4 (t, Pro-C-5), 50.1* (t, Pro-C-5), 30.2* (q, $CH_3N$), 29.7 (q, $CH_3N$), 27.9 (d, Val-C-3), 25.9 (q, $(CH_3)_3C$), 25.8* (q, $(CH_3)_3C$), 19.9* (q, Val-C-4), 19.8 (q, Val-C-4), 19.7* (q, Val-C-4), 19.5 (q, Val-C-4), 18.8 (q, Pro $CH_3C$-3), 18.7* (q, Pro $CH_3C$-3), 18.1 (s, $C(CH_3)_3$), 18.0* (s, $C(CH_3)_3$),-4.66 (q, $CH_3Si$),-4.69* (q, $CH_3Si$),-4.8* (q, $CH_3Si$),-5.0 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity): 659 ($M^+$, 0.1), 549 (8), 486 (18), 364 (14), 248 (59), 220 (20), 176 (47), 91 (100), 84 (23).

**HRMS** *m/z* calcd for $C_{33}H_{49}N_3O_7Si$ 659.3060, found 659.3065 (EI).

**Cbz-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OBt (405)**




**405**

**Procedure:** DCC (0.022 g, 0.106 mmol) was added to a stirred solution of acid **396** (0.012 g, 0.021 mmol) and HOBt (6.0 mg, 0.042 mmol) in $CH_2Cl_2$ (0.3 mL). After 6 h the reaction mixture was diluted with ethyl acetate (0.5 mL). The precipitated DCU was filtered off and the combined filtrate were concentrated, and fractionated by PTLC (60% ethyl acetate in hexane) to give compound **405** (0.013 mg, 90%) as an oil.

$[\alpha]_D$ −65 (*c* 0.25, $CH_2Cl_2$)

**IR** $\nu_{max}$ 1831, 1689, 1652 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 4.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ 8.02 (1H, ddd, *J* = 1, 1, 8 Hz, ArH), 7.73 (1H, ddd, *J* = 1, 1, 8 Hz, ArH), 7.53 (1H, ddd, *J* = 1, 8, 8 Hz, ArH), 7.39 (1H, ddd, *J* = 1, 8, 8 Hz, ArH), 7.38-7.31 (5H, m, PhH), 5.36* (1H, d, *J* = 12.5 Hz, $H_2CPh$), 5.31 (1H, d, *J* = 7.5 Hz, $H_2CO_2$), 5.25* (1H, d, *J* = 7.5 Hz, $H_2CO_2$), 5.17 (1H, d, *J* = 12.5 Hz, $H_2CPh$), 5.14 (1H, d, *J* = 12.5 Hz, $H_2CPh$), 5.07* (1H, d, *J* = 12.5 Hz, $H_2CPh$), 4.81 (, d, *J* = 7.5 Hz, $H_2CO_2$), 4.79* (1H, d, *J* = 7.5 Hz, $H_2CO_2$), 4.63 (1H, s, Pro HC-2), 4.62 (, d, *J* = 11 Hz, Val-HC-2), 4.53 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.43* (1H, d, *J* = 11 Hz, Val-HC-2), 3.94 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-4), 3.70 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.45 (3H, s, $H_3CO$), 3.43* (3H, s, $H_3CO$), 3.00 (3H, s, $H_3CN$), 2.99* (3H, s, $H_3CN$), 2.39-2.28 (1H,

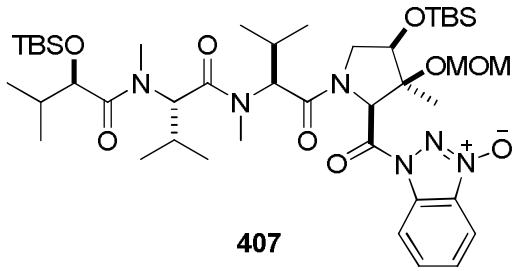
m, Val-HC-3), 1.94 (3H, s, Pro-$H_3CC$-3), 1.70* (3H, s, Pro-$H_3CC$-3), 0.93 (9H, s, $(H_3C)_3C$), 0.90 (3H, d, $J$ = 6.5 Hz, Val-$H_3C$-4), 0.87* (9H, s, $(H_3C)_3C$), 0.88 (3H, d, $J$ = 6.5 Hz, Val-$H_3C$-4), 0.85* (3H, d, $J$ = 6.5 Hz, Val-$H_3C$-4), 0.81* (3H, d, $J$ = 6.5 Hz, Val-$H_3C$-4), 0.16 (3H, s, $H_3CSi$), 0.14 (3H, s, $H_3CSi$), 0.09* (3H, s, $H_3CSi$), 0.00* (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 4.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ 170.8 (s, Val-CO), 164.0 (s, Pro-CO), 157.3 (s, $NCO_2$), 143.6 (s, Ar ), 136.8 (s, Ph), 136.3* (s, Ph), 128.9 (s, Ar), 128.9 (d, Ar), 128.8 (d ×2, Ph), 128.6* (d, Ph), 128.3 (d, Ph), 128.0 (d ×2, Ph), 127.9* (d, Ph), 124.9 (d, Ar), 121.0 (d, Ar), 109.6 (d, Ar), 93.3 (t, $CH_2O_2$), 81.3 (s, Pro-C-3), 81.1* (s, Pro-C-3), 77.32 (d, Pro-C-4), 67.7 (t, $CH_2Ph$), 67.14 (d, Pro-C-2), 67.10 (d, Pro-C-2), 62.1* (d, Val-C-2), 61.5 (d, Val-C-2), 56.4 (q, $CH_3O$), 50.3 (t, Pro-C-5), 29.7 (q, $CH_3N$), 27.9* (d, Val-C-3), 27.8 (d, Val-C-3), 25.9 (q ×3, $(CH_3)_3C$), 25.8* (q ×3, $(CH_3)_3C$), 19.7* (q, Pro-$CH_3C$-3), 19.6 (q, Pro-$CH_3C$-3), 19.3* (q, Val-C-4), 19.1 (q, Val-C-4), 18.8 (q, Val-C-4), 18.7* (q, Val-C-4), 18.1 (s, $C(CH_3)_3$), -4.6 (q, $CH_3Si$), -4.9 (s, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 684 ($[M+1]^+$, 8), 549 (100), 364 (30), 248 (65).

**HRMS** *m/z* calcd for $C_{34}H_{49}N_5O_8Si$ 683.3350 (684.3429 for M+H), found 684.3426 (ESI).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-OBt (407)**:




**407**

**Procedure:** DCC (0.016 g, 0.080 mmol) was added to a stirred solution of acid **399** (0.012 g, 0.016 mmol) and HOBt (4.5 mg, 0.032 mmol) in $CH_2Cl_2$ (0.3 mL). After 6 h the reaction mixture was diluted with ethyl acetate (0.5 mL). The precipitated DCU was

filtered off and the combined filtrate were concentrated, and fractionated by PTLC (60% ethyl acetate in hexane) to give compound **407** (12.5 mg, 91%) as a thick oil.

**$[\alpha]_D$** −70 (*c* 0.40, $CH_2Cl_2$)

**IR** $\nu_{max}$ 1816, 1636 $cm^{-1}$.

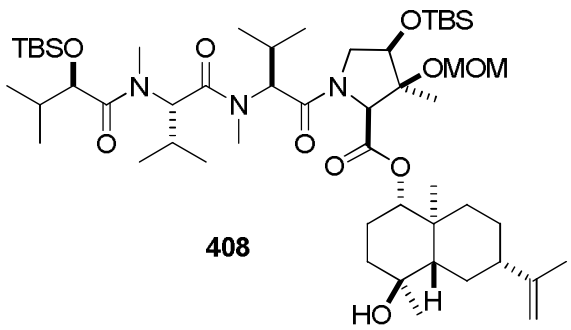
**$^1$H NMR** ( MHz, ) δ 8.02 (1H, d, *J* = 8.5 Hz, ArH), 7.72 (1H, d, *J* = 8.5 Hz, ArH), 7.54 (1H, dd, *J* = 8.5, 8.5 Hz, ArH), 7.40 (1H, dd, *J* = 8.5, 8.5 Hz, ArH), 5.30 (1H, d, *J* = 7.5 Hz, $H_2CO_2$), 5.14 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 5.10 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.81 (1H, d, *J* = 7.5 Hz, $H_2CO_2$), 4.63 (1H, s, Pro-HC-2), 4.57 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-5), 4.12 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.86 (1H, dd, *J* = 6.5, 9.5 Hz, Pro-HC-4), 3.72 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.45 (3H, s, $H_3CO$), 3.26 (3H, s, Val$^1$-$H_3CN$), 3.15 (3H, s, Val$^2$-$H_3CN$), 2.41-2.30 (2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 1.96 (1H, dqq, *J* = 6.5, 6.5, 6.5 Hz, Hmb-HC-3), 1.73 (3H, s, $H_3CC$-3), 0.94 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.93 (9H, s, $(H_3C)_3C$), 0.92 (9H, s, $(H_3C)_3C$), 0.91 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.90 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.88 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.86 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.79 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.16 (3H, s, $H_3CSi$), 0.14 (3H, s, $H_3CSi$), 0.041 (3H, s, $H_3CSi$), 0.029 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.7 (s, Hmb-CO), 172.4 (s, Val$^2$-CO), 170.4 (s, Val$^1$-CO), 164.0 (s, Pro-CO), 143.6 (s, Ar), 128.9 (s & d, Ar ×2), 124.9 (d, Ar), 120.3 (d, Ar), 109.6 (d, Ar), 93.3 (t, $CH_2O2$), 81.3 (s, Pro-C-3), 79.7 (d, Hmb-C-2), 77.5 (d, Pro-C-4), 67.1 (d, Pro-C-2), 58.9 (d, Val$^1$-C-2), 58.7 (d, Val$^2$-C-2), 56.5 (q, $CH_3O$), 50.4 (t, Pro-C-5), 32.0 (d, Hmb-C-3), 31.0 (q, Val$^1$-$CH_3N$), 30.3 (q, Val$^2$-$CH_3N$), 27.9 (d, Val$^1$-C-3), 27.6 (d, Val$^2$-C-3), 26.0 (q ×3, $(CH_3)_3C$), 25.9 (q ×3, $(CH_3)_3C$), 19.82 (q, Hmb-C-4), 19.76 (q, Val-C-4), 19.6 (q, Pro-$CH_3C$-3), 19.0 (q ×2, Val C-4), 18.6 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.2 (s & q, $C(CH_3)_3$ & Hmb C-4), -4.4 (q, $CH_3Si$), -4.6 (q, $CH_3Si$), -4.97 (q, $CH_3Si$), -4.99 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 899 ([M+23]$^+$, 25), 877 ([M+1]$^+$, 45), 742 (100).

**HRMS** *m/z* calcd for $C_{43}H_{76}N_6O_9Si_2$ 877.5212 (877.5290 for M+H), found 877.5259 (ESI).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)(3-Me)Pro-Lar (408)**:




**408**

**Procedure:** PhMgBr (0.6 M in THF; 0.068 mL, 0.04 mmol) was added to a stirred solution of lairdinol A (0.016 g, 0.068 mmol) in THF (0.25 mL) at 0°C. After 30 min. ester **407** (0.030 g, 0.034 mmol) was added as a solution in THF (0.25 mL). The reaction mixture was allowed to reach ambient temperature and subjected to reflux. After 5 h the reaction mixture was cooled down and was quenched with phosphate buffer (pH = 7) and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$, concentrated and fractionated using PTLC (60% EtOAc in hexane) to afford compound **408** (0.013 g, 40%; 20% based on lairdinol A) as a thick oil along with lairdinol A (0.012 g, 75%).

**$[\alpha]_D$** −39 (*c* 0.20, $CH_2Cl_2$)

**IR** (DRIFT) $\nu_{max}$ 3382, 1738, 1636 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.10 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 5.09 (1H, d, *J* = 7 Hz, $OCH_2O$), 5.02 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.72-4.68 (2H, m, Lar-H2C-2), 4.65 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.59 (1H, dd, *J* = 4, 11.5 Hz, Lar-HC-1), 4.41 (1H, dd, *J* = 7, 9.5 Hz, Pro-HC-5), 4.19 (1H, s, Pro-HC-2), 4.10 (1H, d, *J* = 6 Hz, Hmb-HC-2), 3.69 (1H, dd, *J* = 7, 9.5 Hz, Pro-HC-4), 3.57 (1H, dd, *J* = 9.5, 9.5 Hz, Pro-HC-5), 3.29 (3H, s, $H_3CO$), 3.20 (3H, s, Val$^1$-$H_3CN$), 3.13 (3H, s, Val$^2$-$H_3CN$), 2.40-2.18 (2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 2.10-1.53 (10H, m), 1.74 (3H, s, Lar-$H_3C$-13), 1.57 (3H, s, Pro-$H_3CC$-3), 1.40-1.16 (4H, m), 1.13 (3H, s, Lar-$H_3C$-14), 1.03 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.99 (3H, s, Lar-$H_3C$-15), 0.92 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.90 (9H, s, $(H_3C)3C$), 0.89 (9H, s, $(H_3C)3C$), 0.88 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4 or Hmb-$H_3C$-4), 0.87 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4 or Hmb-$H_3C$-4), 0.82 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.78 (3H, d, *J*

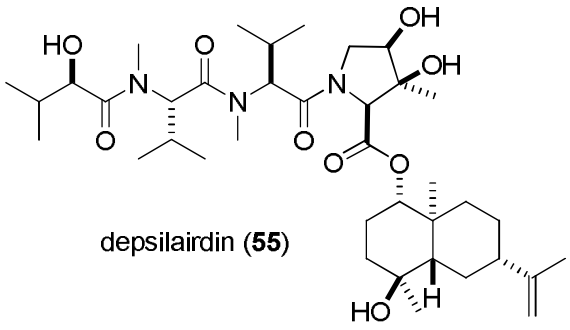
= 6.5 Hz, Val[1]-$H_3C$-4), 0.11 (3H, s, $H_3CSi$), 0.085 (3H, s, $H_3CSi$), 0.029 (3H, s, $H_3CSi$), 0.013 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.5 (s, Hmb-CO), 172.1 (s, Val[2]-CO), 169.8 (s, Val[1]-CO), 166.3 (s, Pro-CO), 150.5 (s, Lar-C-11), 108.6 (t, Lar-C-12), 92.8 (t, $OCH_2O$), 82.5 (d, Lar-C-1), 80.7 (s, Pro-C-3), 79.6 (d, Hmb-C-2), 77.2 (d, Pro-C-4), 71.6 (s, Lar-C-4), 68.1 (d, Pro-C-2), 59.0 (d, Val[1]-C-2), 58.6 (d, Val[2]-C-2), 56.2 (q, $CH_3O$), 53.5 (d, Lar-C-5), 50.5 (t, Pro-C-5), 45.8 (d, Lar-C-7), 40.88 (t, Lar-C-3 or C-9), 40.83 (t, Lar-C-9 or C-3), 38.3 (s, Lar-C-10), 32.0 (d, Hmb-C-3), 31.1 (q, Val[1]-$CH_3N$), 30.2 (q, Val[2]-$CH_3N$), 27.8 (d, Val[1]-C-3), 27.8 (d, Val[2]-C-3), 26.5 (t, Lar-C-8), 26.0 (q, $(CH_3)_3C$), 25.93 (t, Lar-C-6), 25.86 (q, $(CH_3)_3C$), 25.3 (t, Lar-C-2), 22.9 (q, Lar-C-14), 21.3 (q, Lar-C-13), 19.7 (q, Val[2]-C-4), 19.6 (q, Pro-$CH_3C$-3), 19.6 (s, $C(CH_3)_3$), 19.3 (q, C-4 Hmb), 19.0 (q, Val[1]-C-4), 18.7 (q, Val[2]-C-4), 18.4 (q, Val[1]-C-4), 18.1 (q, Hmb-C-4), 18.1 (s, $C(CH_3)_3$), 14.5 (q, Lar-C-15), -4.4 (q, $CH_3Si$), -4.6 (q, $CH_3Si$), -5.01 (q, $CH_3Si$), -5.06 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 1002 ($[M+23]^+$, 85), 980 ($[M+1]^+$, 75), 706 (70), 549 (88), 433 (80), 413 (72), 391 (100), 248 (73), 130 (90).

**HRMS** *m/z* calcd for $C_{52}H_{97}N_3O_{10}Si_2$ 979.6712 (980.6785 for M+H), found 980.6761 (ESI).

**Hmb-MeVal-MeVal-(4-OH)(3-OH)(3-Me)Pro-Lar: depsilairdin (55)**



depsilairdin (**55**)

**Procedure:** TBAF (0.011 g, 0.041 mmol) was added to a stirred solution of **408** (0.0040 g, 0.0041 mmol) in $CH_2Cl_2$ (0.1 mL) at room temperature. After 2 d, the mixture was diluted with $CH_2Cl_2$ and washed with water. The organic layer was dried over $Na_2SO_4$,

concentrated, and fractionated using FCC (50% ethyl acetate in hexane) to afford corresponding diol (0.0030 g, 97%). Dowex 50 (0.050 g) was added to a solution of the intermediate diol (0.0030 g, 0.0040 mmol) in 5 : 1 mixture of MeOH : $H_2O$ (0.5 mL). The reaction mixture was allowed to reflux for 36 h, filtered and washed with MeOH. The organic layer was concentrated and fractionated by [HPTLC-Fertigplatten CN $F_{254}$, 10x10, 0.2 mm] (40% acetonitrile in $H_2O$) to afford **55** (0.0025 g, 85 %) as a thick oil.

**Hmb-MeVal-MeVal-(4-OH)(3-OH)Pro-Lar (Synthetic depsilairdin) (55)**

$[\alpha]_D$ −30 (*c* 0.35, $CH_2Cl_2$)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.13 (1H, d, *J* = 11 Hz), 4.99 (1H, d, *J* = 11 Hz), 4.70 (2H, br s), 4.67 (1H, dd, *J* = 4, 12 Hz), 4.29-4.25 (2H, m), 4.24 (1H, dd, *J* = 5, 11.5 Hz), 3.84-3.78 (1H, m), 3.77-3.72 (1H, m), 3.43 (1H, d, *J* = 7.5 Hz), 3.15 (3H, s), 2.98 (3H, s), 2.39-2.31 (1H, m), 2.31-2.23 (1H, m), 1.95-1.87 (3H, m), 1.87-1.84 (3H, m), 1.84-1.75 (3H, m), 1.73 (3H, s), 1.65-1.50 (3H, m), 1.37 (3H, s), 1.30-1.20 (2H, m), 1.15 (3H, s), 1.09 (3H, d, *J* = 7 Hz), 1.00 (3H, s), 0.97 (3H, d, *J* = 7 Hz), 0.85 (6H, d, *J* = 7 Hz), 0.80 (3H, d, *J* = 7 Hz), 0.77 (3H, d, *J* = 7 Hz).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.0, 172.1, 171.3, 170.4, 150.4, 108.7, 83.6, 76.71, 76.67, 72.9, 71.5, 67.5, 59.3, 58.9, 53.5, 53.2, 45.8, 40.8, 40.5, 38.3, 31.0, 30.9, 30.1, 27.7, 27.6, 26.5, 25.9, 25.4, 25.2, 23.0, 21.3, 20.3, 19.6, 19.3, 18.62, 18.59, 14.7, 14.4.

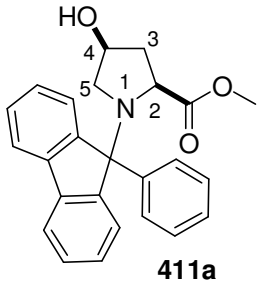
**Hmb-MeVal-MeVal-(4-OH)(3-OH)Pro-Lar (Natural depsilairdin) (55)**

$[\alpha]_D$ −65 (*c* 0.90, $CH_2Cl_2$)

**$^1$H NMR** (500 MHz, C6D6) δ 5.12 (1H, d, *J* = 11 Hz), 4.98 (1H, d, *J* = 11 Hz), 4.69 (2H, br s), 4.67 (1H, dd, *J* = 4, 12 Hz), 4.28-4.24 (2H, m), 4.23 (1H, dd, *J* = 5, 11.5 Hz), 3.83-3.75 (2H, m), 4.45 (1H, br s), 3.14 (3H, s), 2.97 (3H, s), 2.38-2.30 (1H, m), 2.30-2.23 (1H, m), 1.96-1.86 (3H, m), 1.86-1.74 (6H, m), 1.73 (3H, s), 1.62-1.52 (3H, m), 1.37 (3H, s), 1.34-1.20 (2H, m), 1.14 (3H, s), 1.09 (3H, d, *J* = 7 Hz), 1.00 (3H, s), 0.97 (3H, d, *J* = 7 Hz), 0.85 (6H, d, *J* = 7 Hz), 0.79 (3H, d, *J* = 7 Hz), 0.76 (3H, d, *J* = 7 Hz).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.0, 171.8, 171.3, 170.3, 150.4, 108.6, 83.5, 76.6, 76.5, 72.8, 71.5, 67.4, 59.2, 58.9, 53.4, 53.0, 45.7, 40.7, 40.4, 38.3, 31.0, 30.8, 30.1, 27.7, 27.6, 26.4, 25.8, 25.3, 25.1, 22.7, 21.3, 20.3, 19.6, 19.2, 18.60, 18.56, 14.7, 14.4.

**(2S,4S)-methyl-4-hydroxy-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (411a)**




**411a**

**Procedure:** $NaBH_4$ (0.25 g, 6.5 mmol) was added to a stirred solution of **168** (0.50 g, 1.5 mmol) in a mixture of $CH_2Cl_2$ and MeOH (1:1 (v/v); 26 mL) at -78 °C under argon. After 16 h, the reaction was quenched by dropwise addition of acetone (6 mL). The mixture was diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (30 % ethyl acetate in hexane) to afford the title compound **411a** as a foam (0.34 g, 68%) along with **167** (0.14 g, 28%) as a white foam.

**$[\alpha]_D$** +165 (*c* 0.50, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3465, 3056, 1722, 1081, 737 $cm^{-1}$.

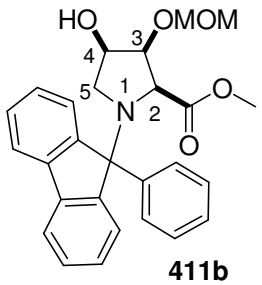
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.79 (1H, ddd, *J* = 1, 1, 8 Hz, ArH), 7.66 (1H, ddd, *J* = 1, 1, 8 Hz, ArH), 7.54-7.59 (2H, m, ArH), 7.43-7.48 (2H, m, ArH), 7.20-7.37 (6H, m, ArH), 7.13 (1H, ddd, *J* = 1, 8, 8 Hz, ArH), 4.30 (1H, d, *J* = 12 Hz, HO), 4.18 (1H, m, HC-4), 3.43 (1H, dd, *J* = 2, 9.5 Hz, HC-5), 3.33 (3H, s, $H_3COC$=O), 3.03 (1H, dd, *J* = 1.5, 11 Hz, HC-2), 2.98 (1H, dd, *J* = 3, 9.5 Hz, HC-5), 1.91 (1H, ddd, *J* = 4, 11, 14 Hz, HC-3), 1.68 (1H, ddd, *J* = 2, 2, 14 Hz, HC-3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 178.7, 148.3, 145.2, 142.1, 142.0, 139.5, 128.9, 128.6, 127.7, 127.63, 127.57, 127.4, 127.0, 126.9, 120.4, 120.2, 75.6, 71.4, 58.2, 57.4, 52.2, 39.3.

**LRMS** (EI), *m/z* (relative intensity):385 ($[M]^+$, 1), 326 (18), 242 (21), 241 (100), 239 (16), 213 (1), 165 (1).

**HRMS** *m/z* calcd for $C_{25}H_{23}NO_3$ 385.1678, found 385.1671.

**(2S,3S,4R)-methyl-4-hydroxy-3-(methoxymethoxy)-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine -2-carboxylate (411b)**




**411b**

**Procedure:** $NaBH_4$ (0.077 g, 2.0 mmol) was added to a stirred solution of **170** (0.18 g, 0.41 mmol) in a mixture of $CH_2Cl_2$ and MeOH (1:1 (v/v); 8 mL) at -78 °C under argon. After 16 h, the reaction was quenched by dropwise addition of acetone (3 mL). The mixture was diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, concentrated, and fractionated by FCC (30 % ethyl acetate in hexane) to afford the title compound **411b** as a foam (0.16 g, 90%) as a white foam.

**$[\alpha]_D$** +175 (*c* 0.83, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3454, 3056, 1727, 1060, 742 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.82 (1H, ddd, *J* = 1, 1, 7.5 Hz, ArH), 7.68 (1H, ddd, *J* = 1, 1, 7.5 Hz, ArH), 7.56-7.60 (2H, m, ArH), 7.50 (1H, ddd, *J* = 1, 7.5, 8.5 Hz, ArH), 7.46

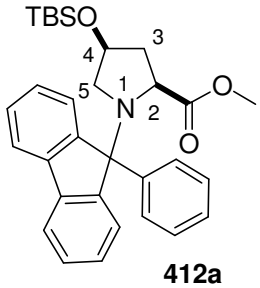
(1H, ddd, *J* = 1, 1, 7.5 Hz, ArH), 7.38 (1H, ddd, *J* = 1, 7.5, 8.5 Hz, ArH), 7.24-7.34 (5H, m, ArH), 7.16 (1H, ddd, *J* = 1, 7.5, 8.5 Hz, ArH), 4.55 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.53 (1H, d, *J* = 9 Hz, HO), 4.48 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.10 (1H, m, HC-4), 3.92 (1H, dd, *J* = 4, 9.5 Hz, HC-3), 3.44 (1H, dd, *J* = 1, 10 Hz, HC-5), 3.37 (3H, s, $H_3COC{=}O$), 3.27 (3H, s, $H_3CO$), 3.20 (1H, d, *J* = 9.5 Hz, HC-2), 2.98 (1H, dd, *J* = 3, 10 Hz, HC-5).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 175.8 (s, $COOCH_3$), 148.1, 144.9, 142.0, 141.1, 139.4, 129.1, 128.68, 128.66, 127.9, 127.75, 127.69, 127.5, 126.9, 126.8, 120.5, 120.2, 95.5 (t, $OCH_2O$), 76.6 (s, C-3), 75.6 (s), 71.3 (d, C-4), 61.1 (d, C-2), 55.9 (q, $CH_3O$), 53.9 (t, C-5), 52.1 (q, $CH_3OC{=}O$).

**LRMS** (EI), *m/z* (relative intensity):445 ($[M]^+$, 1), 387 (4), 242 (22), 241 (100), 239 (18), 213 (1), 165 (1).

**HRMS** *m/z* calcd for $C_{27}H_{27}NO_5$ 445.1889, found 445.1898.

**(2S,4S)-methyl-4-(*t*-butyldimethylsilyloxy)-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (412a)**




**412a**

**Procedure:** 2,6-Lutidine (0.053 mL, 0.050 g, 0.47 mmol) and TBSOTf (0.069 mL, 0.093 g, 0.35 mmol) were sequentially added to a stirred solution of alcohol **411a** (0.090 g, 0.23 mmol) in dry $CH_2Cl_2$ (2.5 mL) at 0 °C. After 15 min, the mixture was diluted with ethyl acetate and washed sequentially with sat. $NaHCO_3$, 5% aq. HCl, sat. $NaHCO_3$ and brine.

The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (20 % ethyl acetate in hexane) to afford the title compound **412a** (0.11 g, 96%) as a white foam.

**$[\alpha]_D$** +129 (*c* 1.55, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3065, 1750, 1020, 733 $cm^{-1}$.

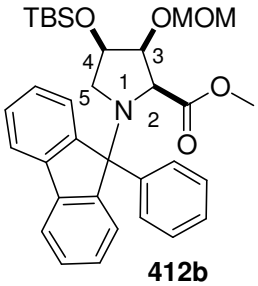
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.74 (1H, d, *J* = 7.5 Hz, ArH), 7.62 (1H, d, *J* = 7.5 Hz, ArH), 7.55-7.60 (2H, m, ArH), 7.50 (1H, d, *J* = 7.5 Hz, ArH), 7.44 (1H, ddd, *J* = 1, 7.5, 7.5 Hz, ArH), 7.30-7.35 (2H, m, ArH), 7.20-7.30 (4H, m, ArH), 7.13 (1H, ddd, *J* = 1, 7.5, 7.5 Hz, ArH), 4.10 (1H, ddd, *J* = 6.5, 6.5, 13 Hz, HC-4), 3.40 (3H, s, $H_3COC$=O), 3.22-3.31 (2H, m, H2C-5), 3.11 (1H, dd, *J* = 7.5, 7.5 Hz, HC-2), 2.02 (1H, ddd, *J* = 6.5, 7.5, 13 Hz, HC-3), 1.84 (1H, ddd, *J* = 7.5, 7.5, 13 Hz, HC-3), 0.87 (9H, s, $(H_3C)_3C$), 0.016 (3H, s, $H_3CSi$),-0.003 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 176.0 (s, C=O), 148.2, 147.3, 143.9, 142.0, 139.6, 128.9, 128.5, 128.0, 127.5, 127.4, 127.3, 125.9, 120.2, 119.9, 77.4, 70.9 (d, C-4), 60.1 (d, C-2), 58.0 (t, C-5), 51.5 (q, $CH_3OC$=O), 40.4 (t, C-3), 25.9 (q, $(CH_3)_3C$), 18.2 (s, $C(CH_3)_3$),-4.6 (q ?2, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):499 ($[M]^+$, 1), 440 (15), 242 (22), 241 (100), 226 (1), 142 (2), 89 (1), 73 (4).

**HRMS** *m/z* calcd for $C_{31}H_{37}NO_3Si$ 499.2543, found 499.2552.

**(2S,3S,4R)-methyl-4-(*t*-butyldimethylsilyloxy)-3-(methoxymethoxy)-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylate (412b)**




**412b**

**Procedure:** 2,6-Lutidine (0.048 mL, 0.046 g, 0.43 mmol) and TBSOTf (0.063 mL, 0.084 g, 0.32 mmol) were sequentially added to a stirred solution of alcohol **411b** (0.095 g, 0.21 mmol) in dry $CH_2Cl_2$ (2 mL) at 0 °C. After 15 min, the mixture was diluted with ethyl acetate and washed sequentially with sat. $NaHCO_3$, 5% aq. HCl, sat. $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (20 % ethyl acetate in hexane) to afford the title compound **412b** (0.11 g, 93%) as a white foam.

**$[\alpha]_D$** +187 (*c* 0.65, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 3065, 1762, 1032, 739 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 7.79 (1H, ddd, *J* = 1, 1, 7.5 Hz, Ar), 7.58-7.67 (2H, m, Ar), 7.47-7.53 (2H, m, Ar), 7.36 (1H, ddd, *J* = 1, 7.5, 8.5 Hz, Ar), 7.23-7.34 (5H, m, Ar), 7.10 (1H, ddd, *J* = 1, 7.5, 8.5 Hz, Ar), 4.80 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.56 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.02 (1H, dd, *J* = 4, 5.5 Hz, HC-3), 3.85 (1H, ddd, *J* = 3, 7, 10 Hz, HC-4), 3.47 (1H, dd, *J* = 10, 11.5 Hz, HC-5), 3.43 (3H, s, $H_3COC$=O), 3.27 (1H, dd, *J* = 7, 11.5 Hz, HC-5), 3.20 (3H, s, $H_3CO$), 3.16 (1H, d, *J* = 5.5 Hz, HC-2), 0.84 (9H, s, $(H_3C)_3C$), 0.011 (3H, s, $H_3CSi$), 0.003 (3H, s, $H_3CSi$).

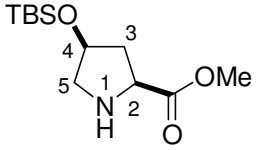
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 172.2 (s, COOCH3), 147.5, 146.2, 143.6, 142.6, 139.2, 129.2, 128.6, 128.3, 128.0, 127.6, 127.5, 127.2, 125.7, 120.3, 119.7, 77.7 (s, C-3), 77.6,

72.7 (d, C-4), 64.0 (d, C-2), 55.7 (q, $CH_3O$), 54.2 (t, C-5), 51.3 (q, $CH_3OC=O$), 25.9 (q, $(CH_3)_3C$), 18.1 (s, $C(CH_3)_3$),-4.5 (q, $CH_3Si$),-4.7 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):559 ($[M]^+$, 0.5), 500 (9), 328 (3), 242 (22), 241 (100), 239 (6), 187 (2), 89 (1).

**HRMS** *m/z* calcd for $C_{33}H_{41}NO_5Si$ 559.2754, found 559.2737.

**Methyl (2S,4S)-4-(tert-butyldimethylsilyloxy)pyrrolidine-2-carboxylate [(4-OTBS)Pro-OMe] (413a)**




**413a**

**Procedure:** Using the same procedure as described for the preparation of **385a**, hydrogenolysis of **412a** (0.10 g, 0.20 mmol) gave **413a** (0.047 g, 90%) after fractionation of the crude by FCC (5% MeOH in $CH_2Cl_2$) pale yellow oil.

**$[\alpha]_D$** −15 (*c* 0.40, $CH_2Cl_2$)

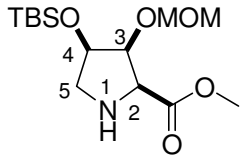
**IR** $\nu_{max}$ 1730, 1060 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.29-4.25 (1H, m, HC-4), 3.81-3.74 (1H, m, HC-2), 3.72 (3H, s, $H_3CO$), 2.97 (1H, br d, *J* = 11.5 Hz, HC-5), 2.90-2.83 (1H, m, HC-5), 2.39 (1H, br s, HN), 2.18 (1H, ddd, *J* = 4.5, 9.5, 13.5 Hz, HC-3), 2.02 (1H, dddd, *J* = 2, 3.5, 3.5, 13.5 Hz, HC-3), 0.84 (9H, s, $(H_3C)_3C$), 0.029 (3H, s, $H_3CSi$), 0.019 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.4 (s, C=O), 72.2 (d, C-4), 59.0 (d, C-2), 56.1 (t, C-5), 52.3 (q, $CH_3O$), 40.0 (t, C-3), 25.8 (q ×3, $(CH_3)_3C$), 18.0 (s, $C(CH_3)_3$), -4.6 (q, $CH_3Si$), -4.7 (q, $CH_3Si$).

**HRMS** *m/z* calcd for $C_{12}H_{25}NO_3Si$ 259.1604 (260.1676 for M+H), found 260.1685 (ESI).

**(2*S*,3*S*,4*R*)-Methyl-4-(*t*-butyldimethylsilyloxy)-3-(methoxymethoxy)pyrrolidine-2-carboxylate (413b)**




**413b**

**Procedure:** Using the same procedure as described for the preparation of **385a**, hydrogenolysis of **412b** (0.040 g, 0.071 mmol) gave **413b** (0.020 g, 90%) after fractionation of the crude by FCC (5% MeOH in $CH_2Cl_2$) as a pale yellow oil.

**$[\alpha]_D$** −69 (*c* 0.60, $CH_2Cl_2$)

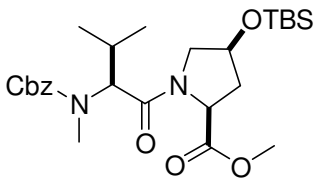
**IR** $\nu_{max}$: 1743, 1038 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.91 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.65 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.26-4.32 (1H, m, HC-4), 4.24 (1H, dd, *J* = 3.5, 4.5 Hz, HC-3), 3.92 (1H, d, *J* = 4.5 Hz, HC-2), 3.77 (3H, s, $H_3COC$=O), 3.33 (3H, s, $H_3CO$), 3.00-3.10 (2H, m, 2XHC-5), 2.05 (1H, br s, HN), 0.89 (9H, s, $(H_3C)_3C$), 0.079 (3H, s, $H_3CSi$), 0.070 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 171.8 (s, COOCH3), 96.7 (t, $OCH_2O$), 77.7 (d, C-3), 75.0 (d, C-4), 62.5 (d, C-2), 55.9 (q, $CH_3O$), 52.3 (q, $CH_3OC$=O), 50.5 (t, C-5), 25.9 (q, $(CH_3)_3C$), 18.2 (s, $C(CH_3)_3$),-4.5 (q, $CH_3Si$),-4.8 (q, $CH_3Si$).

**HRMS** *m/z* calcd for $C_{14}H_{29}NO_5Si$ 319.1815 (320.1888 for M+H), found 320.1900 (CI+).

**Cbz-MeVal-(*cis*-4-OTBS)Pro-OMe (414a)**




**414a**

**Procedure:** Using the same procedure as described for the preparation of **391a**, PyBroP (1.3 g, 0.27 mmol), DIPEA (0.63 mL, 0.47 g, 0.36 mmol) mediated coupling of **413a** (0.47 g, 0.18 mmol) with Cbz-MeVal-OH (**60**) (0.63 g, 0.23 mmol) gave **414a** (0.80 g, 87%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a white solid.

**$[\alpha]_D$** −63 (*c* 0.74, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1750, 1690, 1642, 1020, 769 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.40 (5H, m, Ph), 5.23* (1H, d, *J* = 12 Hz), 5.14 (d, *J* = 12.6 Hz), 5.11 (d, *J* = 12.6 Hz), 5.08* (2H, d, *J* = 12 Hz, $H_2CPh$), 4.59 (1H, dd, *J* = 4, 9 Hz, Pro-HC-2), 4.56 (d, *J* = 11 Hz), 4.31* (1H, d, *J* = 11 Hz, Val-HC-2), 4.36-4.41 (m), 4.06-4.10* (1H, m, Pro-HC-4), 3.69 (s), 3.66* (3H, s, $H_3COC$=O), 3.53 (dd, *J* = 3, 10.5 Hz), 3.27* (3H, dd, *J* = 3, 10.5 Hz, Pro-HC-5), 2.98 (s), 2.97* (3H, s, $H_3CN$), 2.21-2.34 (2H, m, Pro-HC-3, Val-C-3), 2.11 (1H, ddd, *J* = 4, 4, 13 Hz, Pro-HC-3), 2.01-2.09 (1H, m, Pro-HC-3), 1.07 (d, *J* = 7 Hz), 1.00* (3H, d, *J* = 7 Hz, Val-$H_3C$-4), 0.90 (d, *J* = 7 Hz), 0.88* (3H, d, *J* = 7 Hz, Val-$H_3C$-4), 0.85 (s), 0.81* (9H, s, $(CH_3)_3C$), 0.57 (s),-0.02* (3H, s, $H_3CSi$), 0.43 (s),-0.04* (3H, s, $H_3CSi$).

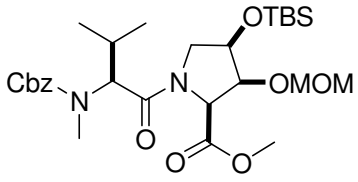
**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.5:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 171.6 (s, Pro-CO), 171.4* (s, Pro-CO), 170.4 (s, Val-C-1), 169.6* (s, Val-C-1), 157.4 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.8 (s, Ph), 136.5* (s, Ph),

128.8* (d, Ph), 128.6 (d, Ph), 128.55* (d, Ph), 128.50* (d, Ph), 128.2 (d, Ph), 127.8 (d, Ph), 70.83 (d, Pro-C-4), 70.75* (d, Pro-C-4), 67.8* (t, $CH_2Ph$), 67.5 (t, $CH_2Ph$), 62.0* (d, Val-C-2), 61.6 (d, Val-C-2), 57.5* (d, Pro-C-2), 57.4 (d, Pro-C-2), 55.6 (t, Pro-C-5), 55.2* (t, Pro-C-5), 52.2 (q, $CH_3OC=O$), 38.2 (t, Pro-C-3), 38.1* (t, Pro-C-3), 30.0* (q, $CH_3N$), 29.7 (q, $CH_3N$), 28.1 (d, Val-C-3), 25.71 (q, $(CH_3)_3C$), 25.67* (q, $(CH_3)_3C$), 19.1* (q, Val-C-4), 19.05 (q, Val-C-4), 19.00* (q, Val-C-4), 18.8 (q, Val-C-4), 18.00 (q, $C(CH_3)_3$), 17.95* (q, $C(CH_3)_3$),-4.8 (q, $CH_3Si$),-4.9* (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):506 ($[M]^+$, 1.5), 449 (34), 220 (33), 176 (51), 126 (4), 91 (100), 73 (12).

**HRMS** *m/z* calcd for $C_{26}H_{42}N_2O_6Si$ 506.2812, found 506.2825.

**Cbz-MeVal-(4-OTBS)(3-OMOM)Pro-OMe (414b)**




**414b**

**Procedure:** Using the same procedure as described for the preparation of **391a**, PyBroP (0.046 g, 0.098 mmol), DIPEA (0.023 mL, 0.017 g, 0.13 mmol) mediated coupling of **413b** (0.021 g, 0.066 mmol) with Cbz-MeVal-OH (0.0.023 g, 0.085 mmol) gave **414b**(0.031 g, 84%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a white solid.

**$[\alpha]_D$** = -93 (*c* 1.0, $CH_2Cl_2$)

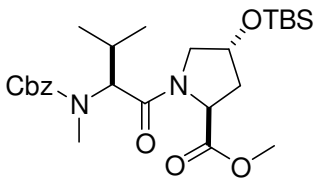
**IR** $\nu_{max}$ 1755, 1690, 1654, 1026 $cm^{-1}$.

**$^{1}$H NMR** (500 MHz, $CDCl_3$) (an ca. 4.8:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.40 (5H, m, Ph), 5.28* (d, *J* = 12 Hz), 5.06-5.20 (2H, m, $H_2CPh$), 4.92 (d, *J* = 7 Hz), 4.84* (1H, d, *J* = 7 Hz, $OCH_2O$), 4.67 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.62 (d, *J* = 6 Hz), 4.60* (1H, d, *J* = 6 Hz, Pro-HC-2), 4.56 (1H, d, *J* = 11 Hz, Val-HC-2), 4.42 (1H, dd, *J* = 4, 6 Hz), 4.31* (dd, *J* = 4,6 Hz, Pro-HC-3), 4.37 (1H, dd, *J* = 7, 9 Hz, Pro-HC-5), 4.11-4.18 (m), 4.01-4.06* (1H, m, Pro-HC-4), 3.74 (s), 3.73* (3H, s, $H_3COC$=O), 3.55 (dd, *J* = 9, 9 Hz), 3.48* (1H, dd, *J* = 9, 9 Hz, Pro-HC-5), 3.34 (3H, s, $H_3CO$), 2.95 (3H, s, $H_3CN$), 2.21-2.35 (1H, m, Val-HC-3), 1.04 (d, *J* = 6.5 Hz), 1.00* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.87-0.93 (12 H, m, Val-$H_3C$-4 & $(H_3C)_3C$), 0.84* (s, $(H_3C)_3C$), 0.12 (s), 0.021* (3H, s, $H_3CSi$), 0.093 (s),-0.025* (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 4.8:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 170.4 (s, Pro-CO), 169.5* (s, Pro-CO), 167.7 (s, Val CO), 167.6* (s, Val CO), 157.3 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.9 (s, Ph), 136.5* (s, Ph), 128.8* (d, Ph), 128.7 (d, Ph), 128.5* (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 127.8* (d, Ph), 96.7 (t, $OCH_2O$), 96.6* (t, $OCH_2O$), 74.7 (d, Pro-C-3), 74.6* (d, Pro-C-3), 72.5 (d, Pro-C-4), 72.4* (d, Pro-C-4), 67.8* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 61.9* (d, Val-C-2), 61.5 (d, Val-C-2), 61.3 (d, Pro-C-2), 61.1* (d, Pro-C-2), 56.10* (q, $CH_3O$), 56.07 (q, $CH_3O$), 52.2 (q, $CH_3OC$=O), 50.6* (t, Pro-C-5), 50.4 (t, Pro-C-5), 30.1* (q, $CH_3N$), 29.6 (q, $CH_3N$), 28.1* (d, Val-C-3), 28.0 (d, Val-C-3), 25.9 (q, $(CH_3)_3C$), 25.8* (q, $(CH_3)_3C$), 19.2* (q, Val-C-4), 19.0 (q, Val-C-4), 18.9 (q, Val-C-4), 18.2 (s, $C(CH_3)_3$), 18.1* (s, $C(CH_3)_3$),-4.7 (q, $CH_3Si$),-4.81* (q, $CH_3Si$),-4.83* (q, $CH_3Si$),-4.9 (q, $CH_3Si$).

**HRMS** *m/z* calcd for $C_{28}H_{46}N_2O_8Si$ 566.3023 (567.3096 for M+H), found 566.3108 (ESI).

**Cbz-MeVal-(*trans*-4-OTBS)Pro-OMe (414c)**




**414c**

**Procedure:** Using the same procedure as described for the preparation of **391a**, PyBroP (1.24 g, 2.66 mmol), DIPEA (0.630 mL, 0.458 g, 3.55 mmol) mediated coupling of **413c** (0.460 g, 0.177 mmol) with Cbz-MeVal-OH (**60**) (0.612 g, 2.30 mmol) gave **414c** (0.764 g, 85%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a white solid.

**$[\alpha]_D$** −93 (*c* 1.5, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1748, 1695, 1646, 1017 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.26-7.42 (5H, m, Ph), 5.27* (1H, d, *J* = 12.5 Hz, $CH_2Ph$), 5.22 (1H, d, *J* = 12.5 Hz, $CH_2Ph$), 5.08* (1H, d, *J* = 12.5 Hz, $CH_2Ph$), 5.05 (1H, d, *J* = 12.5 Hz, $CH_2Ph$), 4.58 (1H, d, *J* = 11 Hz, Val-HC-2), 4.56 (1H, dd, *J* = 7.5, 8.5 Hz, Pro-HC-2), 4.51-4.47 (1H, m, Pro-HC-4), 4.46-4.41* (1H, m, Pro-HC-4), 4.37* (1H, d, *J* = 11 Hz, Val-HC-2), 3.93 (1H, ddd, *J* = 2, 2, 11 Hz, Pro-HC-5), 3.78-3.75 (1H, m, Pro-HC-5), 3.75 (3H, s, $H_3CO$), 3.74* (3H, s, $H_3CO$), 3.67* (1H, dd, *J* = 4.5, 10.5 Hz, Pro-HC-5), 3.51-3.46* (1H, m, Pro-HC-5), 2.92 (3H, s, $H_3CN$), 2.91* (3H, s, $H_3CN$), 2.40-2.26 (1H, m, Val-HC-3), 2.26-2.19 (1H, m, Pro-HC-3), 2.19-2.12* (1H, m, Pro-HC-3), 1.99 (1H, ddd, *J* = 4, 9, 13 Hz, Pro-HC-3), 0.99 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.98* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.88 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.87* (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.86* (9H, s, $(H_3C)3C$), 0.85 (9H, s, $(H_3C)3C$), 0.086 (3H, s, $H_3CSi$), 0.066 (3H, s, $H_3CSi$), 0.050* (3H, s, $H_3CSi$), 0.019* (3G, s, $H_3CSi$).

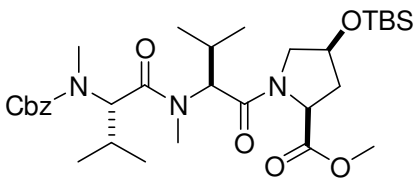
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 172.6 (s, Pro-CO), 172.5* (s, Pro-CO), 169.6 (s, Val-CO), 168.8* (s, Val-CO), 157.0 (s, NCO2), 155.8* (s, NCO2), 136.6 (s, Ph), 136.3* (s, Ph), 128.6* (d, Ph), 128.5 (d, Ph), 128.2* (d, Ph), 128.0* (d, Ph), 127.9 (d, Ph), 127.6 (d, Ph), 70.7 (d, Pro-C-4), 70.4* (d, Pro-C-4), 67.7* (t, $CH_2Ph$), 67.3 (t, $CH_2Ph$), 62.1* (t,

Val-C-2), 61.7 (t, Val-C-2), 57.8 (d, Pro-C-2), 55.6 (t, Pro-C-5), 54.8* (t, Pro-C-5), 52.15* (q, $CH_3O$), 52.09 (q, $CH_3O$), 38.3 (t, Pro-C-3), 37.9* (t, C-3 Pro), 29.6* (q, $CH_3N$), 29.3 (q, $CH_3N$), 27.5 (d, Val-C-3), 27.4 (d, Val-C-3), 25.5 (q, $(CH_3)_3C$), 19.0 (q, Val-C-4), 18.4 (q, Val-C-4), 17.8 (s, $C(CH_3)_3$), 17.2* (q, Val-C-4), 16.1* (q, Val-C-4), -4.90* (q, $CH_3Si$), -4.94 (q, $CH_3Si$), -4.97* (q, $CH_3Si$), -5.05 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 529 ($[M+23]^+$, 5), 507 ($[M+1]^+$, 100), 146 (3).

**HRMS** *m/z* calcd for $C_{26}H_{42}N_2O_6Si$ 506.2818 (507.2890 for M+H), found 507.2872 (ESI).

**Cbz-MeVal-MeVal-(*cis*-4-OTBS)Pro-OMe (415a)**




**415a**

**Procedure:** Using the same procedure as described for the preparation of **392a**, hydrogenolysis of **414a** (0.060 g, 0.12 mmol) followed by PyBroP (0.088 g, 0.19 mmol), DIPEA (0.044 mL, 0.033 g, 0.25 mmol) mediated coupling with Cbz-MeVal-OH (0.044 g, 0.16 mmol) gave **415a** (0.066 g, 85%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick oil.

**$[\alpha]_D$** −79 (*c* 2.2, $CH_2Cl_2$)

**IR** $\nu_{max}$: 1738, 1696, 1642 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.38 (5H, m, Ph), 5.22* (d, *J* = 12 Hz), 5.17 (d, *J* = 12.5 Hz), 5.14 (d, *J* = 12.5 Hz), 5.09* (2H, d, *J* = 12 Hz, H3CPh), 5.00 (d, *J* = 11 Hz), 4.96* (1H, d, *J* = 11 Hz, $Val^2$-HC -2), 4.73 (d, *J* = 11 Hz), 4.48* (1H, d, *J* = 11 Hz, $Val^1$-

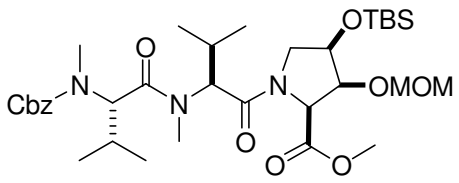
HC- 2), 4.55 (dd, *J* = 5, 9 Hz), 4.52* (1H, dd, *J* = 5, 9 Hz, Pro-HC-2), 4.30-4.38 (1H, m, Pro-HC-4), 4.09 (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 3.69 (s), 3.68* (3H, s, $H_3COC{=}O$), 3.52 (1H, dd, *J* = 4.5, 10.5 Hz, Pro-HC-5), 3.09 (s), 2.90* (3H, s, $H_3CN$), 2.85 (s), 2.83* (3H, s, $H_3CN$), 2.17-2.38 (3H, m, $Val^1$-HC- 3, $Val^2$-HC -3, Pro-HC-3), 2.07 (1H, ddd, *J* = 5, 5, 13 Hz, Pro-HC-3), 1.04 (d, *J* = 7 Hz), 1.03* (3H, d, *J* = 7 Hz, Val-$H_3C$-4), 0.81-0.88* (15H, m, $(H_3C)_3C$, Val-$H_3C$-4x2), 0.80* (d, *J* = 7 Hz, Val-$H_3C$-4), 0.76 (d, *J* = 7 Hz), 0.047 (s), 0.041* (3H, s, $H_3CSi$), 0.035 (s), 0.027* (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 171.6 (s, $Val^1$-C- 1), 171.5* (s, $Val^1$-C- 1), 171.4 (s, $Val^2$-C- 1), 170.9* (s, $Val^2$-C- 1), 169.9* (s, Pro-CO), 169.7 (s, Pro-CO), 157.1 (s, $NCO_2$), 156.1* (s, $NCO_2$), 136.9 (s, Ph), 136.2* (s, Ph), 128.8* (d, Ph), 128.67* (d, Ph), 128.65 (d, Ph), 128.61* (d, Ph), 128.2 (d, Ph), 128.7 (d, Ph), 70.7 (d, Pro-C-4), 68.0* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 61.2* (d, $Val^2$-C- 2), 60.7 (d, $Val^2$-C- 2), 59.4 (d, $Val^1$-C- 2), 57.4 (d, Pro-C-2), 55.4* (t, Pro-C-5), 55.3 (t, Pro-C-5), 52.2 (q, $CH_3OC{=}O$), 38.1 (t, Pro-C-3), 30.7 (q, $CH_3N$), 30.3* (q, $CH_3N$), 29.8* (q, $CH_3N$), 29.4 (q, $CH_3N$), 28.0* (d, $Val^2$-C- 3), 27.9 (d, $Val^2$-C- 3), 27.6* (d, $Val^1$-C- 3), 27.5 (d, $Val^1$-C- 3), 25.7 (q, $(CH_3)_3C$), 20.0* (q, $Val^1$-C- 4), 19.8 (q, $Val^1$-C- 4), 19.0 (q, $Val^2$-C- 4), 18.86* (q, $Val^2$-C- 4), 18.84* (q, $Val^2$-C- 4), 18.6 (q, $Val^2$-C- 4), 18.4* (q, $Val^1$-C- 4), 18.3 (q, $Val^1$-C- 4), 18.0 (s, $C(CH_3)_3$),-4.8 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):619 ($[M]^+$, 1), 399 (3), 313 (2), 270 (12), 220 (22), 176 (43), 91 (100).

**HRMS** *m/z* calcd for $C_{32}H_{53}N_3O_7Si$ 619.3653, found 619.3664.

**Cbz-MeVal-MeVal-(4-OTBS)(3-MOM)Pro-OMe (415b)**




**415b**

**Procedure:** Using the same procedure as described for the preparation of **392a**, hydrogenolysis of **414b** (0.030 g, 0.053 mmol) followed by PyBroP (0.037 g, 0.079 mmol), DIPEA (0.018 mL, 0.014 g, 0.11 mmol) mediated coupling with Cbz-MeVal-OH (0.018 g, 0.069 mmol) gave **415b** (0.031 g, 87%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick oil.

**$[\alpha]_D$** −100 (*c* 0.67, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1773, 1731, 1690, 1638, 1020 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.3:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 7.28-7.39 (5H, m, Ph), 5.24* (d, *J* = 12 Hz), 5.18 (d, *J* = 12.5 Hz), 5.14 (d, *J* = 12.5 Hz), 5.09* (2H, d, *J* = 12 Hz, $H_2CPh$), 5.01 (d, *J* = 11 Hz), 4.97* (1H, d, *J* = 11 Hz, Val$^2$-HC -2), 4.91 (d, *J* = 7 Hz), 4.90* (1H, d, *J* = 7 Hz, $OCH_2O$), 4.72 (d, *J* = 11 Hz), 4.47* (1H, d, *J* = 11 Hz, Val$^1$-HC- 2), 4.66 (d, *J* = 7 Hz), 4.65* (1H, d, *J* = 7 Hz, $OCH_2O$), 4.60 (d, *J* = 6 Hz), 4.55* (1H, d, *J* = 6 Hz, Pro-HC-2), 4.35-4.41 (2H, m, Pro-HC-3, Pro-HC-5), 4.03-4.12 (1H, m, Pro-HC-4), 3.74 (s), 3.73* (3H, s, $H_3COC$=O), 3.57 (1H, dd, *J* = 9, 9 Hz, Pro-HC-5), 3.33 (s), 3.32* (3H, s, $H_3CO$), 3.08 (s), 2.87* (3H, s, $H_3CN$), 2.86 (s), 2.85* (3H, s, $H_3CN$), 2.12-2.40 (2H, m, Val 1, Val$^2$-HC -3), 1.02 (d, *J* = 7 Hz), 1.01* (3H, d, *J* = 7 Hz, Val$^1$-$H_3C$-4), 0.89 (s), 0.88* (9H, s, $(H_3C)_3C$), 0.87 (d, *J* = 7 Hz), 0.84* (3H, d, *J* = 7 Hz, Val$^1$-$H_3C$-4), 0.85 (d, *J* = 7 Hz), 0.80* (3H, d, *J* = 7 Hz, Val$^2$-$H_3C$-4), 0.76 (d, *J* = 7 Hz), 0.75* (3H, d, *J* = 7 Hz, Val$^2$-$H_3C$-4), 0.11, 0.10* (3H, s, $H_3CSi$), 0.085 (s), 0.076* (3H, s, $H_3CSi$).

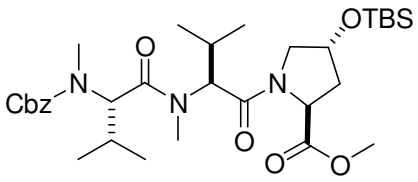
**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.3:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ: 171.5 (s, Val$^1$-C- 1), 170.9* (s, Val$^1$-C- 1), 170.1* (s,

$Val^2$-C- 1), 169.9 (s, $Val^2$-C- 1), 167.61 (s, Pro-CO), 167.58* (s, Pro-CO), 157.1 (s, $NCO_2$), 156.2* (s, $NCO_2$), 136.9 (s, Ph), 136.2* (s, Ph), 128.8* (d, Ph), 128.71* (d, Ph), 128.68 (d, Ph), 128.6* (d, Ph), 128.2 (d, Ph), 128.8 (d, Ph), 96.74 (t, $OCH_2O$), 96.71* (t, $OCH_2O$), 74.70 (d, Pro-C-3), 74.64* (d, Pro-C-3), 72.6 (d, Pro-C-4), 72.5* (d, Pro-C-4), 68.1* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 61.5 (d, Pro-C-2), 61.4* (d, Pro-C-2), 61.2* (d, $Val^2$-C- 2), 60.7 (d, $Val^2$-C- 2), 59.23* (d, $Val^1$-C- 2), 59.2 (d, $Val^1$-C- 2), 56.1 (q, $CH_3O$), 52.2 (q, $CH_3OC=O$), 50.4* (t, Pro-C-5), 50.3 (t, Pro-C-5), 30.7 (q, $CH_3N$), 30.3* (q, $CH_3N$), 29.9* (q, $CH_3N$), 29.5 (q, $CH_3N$), 28.05* (d, $Val^2$-C- 3), 28.98 (d, $Val^2$-C- 3), 27.7* (d, $Val^1$-C- 3), 27.6 (d, $Val^1$-C- 3), 25.9 (q, $(CH_3)_3C$), 20.2* (q, $Val^1$-C- 4), 20.0 (q, $Val^1$-C- 4), 19.0 (q, $Val^2$-C- 4), 18.9* (q, $Val^2$-C- 4), 18.8* (q, $Val^2$-C- 4), 18.5 (q, $Val^2$-C- 4), 18.4* (q, $Val^1$-C- 4), 18.3 (q, $Val^1$-C- 4), 18.2 (s, $C(CH_3)_3$),-4.7 (q, $CH_3Si$),-5.0 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 702 ($[M+23]^+$, 65), 680 ($[M+1]^+$, 98), 523 (20), 361 (100).

**HRMS** *m/z* calcd for $C_{34}H_{57}N_3O_9Si$ 679.3864 (680.3937 for M+H), found 680.3954 (ESI).

**Cbz-MeVal-MeVal-(*trans*-4-OTBS)Pro-OMe (415c)**




**415c**

**Procedure:** Using the same procedure as described for the preparation of **392a**, hydrogenolysis of **412b** (0.45 g, 0.89 mmol) followed by PyBroP (0.63 g, 1.3 mmol), DIPEA (0.32 mL, 0.23 g, 0.18 mmol) mediated coupling with Cbz-MeVal-OH (0.31 g, 1.2 mmol) gave **413b** (0.48 g, 87%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick oil.

**[α]$_D$** −147 (*c* 0.95, $CH_2Cl_2$)

**IR** $\nu_{max}$: 1748, 1700, 1635 $cm^{-1}$.

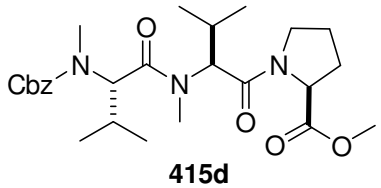
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.26-7.35 (5H, m, Ph), 5.21* (1H, d, *J* = 12 Hz, $H_2CPh$), 5.14 (1H, d, *J* = 12.5 Hz, $H_2CPh$), 5.12 (1H, d, *J* = 12.5 Hz, $H_2CPh$), 5.05* (1H, d, *J* = 12 Hz, $H_2CPh$), 4.98 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.95* (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.71 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.40-4.50 (2H, m, Pro-HC-2, HC-4), 3.72-3.81 (2H, m, Pro-$H_2C$-5), 3.71 (3H, s, $H_3CO$), 3.70* (3H, s, $H_3CO$), 3.07 (3H, s, Val$^1$-$H_3CN$), 2.87* (3H, s, Val$^1$-$H_3CN$), 2.83 (3H, s, Val$^2$-$H_3CN$), 2.82* (3H, s, Val$^2$-$H_3CN$), 2.20-2.35 (2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 2.08-2.19 (1H, m, Pro-HC-3 ), 1.91-2.01 (1H, m, Pro-HC-3 ), 0.95 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.94* (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.77-0.86 (15H, m, $(H_3C)_3C$,Val$^2$-$H_3C$-4), 0.71 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.70* (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.037 (3H, s, $H_3CSi$), 0.030* (3H, s, $H_3CSi$), 0.019 (3H, s, $H_3CSi$), 0.010* (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 172.7 (s, Pro-CO), 172.6* (s, Pro-CO), 171.2 (s, Val$^2$-CO), 170.6* (s, Val$^2$-CO), 169.8* (s, Val$^1$-CO), 169.7 (s, Val$^1$-CO), 157.8 (s, NCO2), 156.1* (s, $NCO_2$), 136.9 (s, Ph), 136.2* (s, Ph), 128.8* (d, Ph), 128.7* (d, Ph), 128.62 (d, Ph), 128.58* (d, Ph), 128.1 (d, Ph), 127.7 (d, Ph), 70.8 (d, Pro-C-4), 68.0* (t, $CH_2Ph$), 67.5 (t, $CH_2Ph$), 61.1* (d, Val$^2$-C-2), 60.7 (d, Val$^2$-C-2), 59.3 (d, Val$^1$-C-2), 58.2 (d, Pro-C-2), 55.94* (t, Pro-C-5), 55.85 (t, Pro-C-5), 52.3 (q, $CH_3O$), 38.50* (t, Pro-C-3), 38.47 (t, Pro-C-3), 30.7 (q, Val$^1$-$CH_3N$), 30.3* (q, Val$^1$-$CH_3N$), 29.8* (q, Val$^2$-$CH_3N$), 29.4 (q, Val$^2$-$CH_3N$), 28.0* (d, Val$^1$-C-3), 27.9 (d, Val$^1$-C-3), 27.5* (d, Val$^2$-C-3), 27.4 (d, Val$^2$-C-3), 25.9 (q, $(CH_3)_3C$), 20.2* (q, Val$^2$-C-4), 20.0 (q, Val$^2$-C-4), 19.1 (q, Val$^1$-C-4), 19.0* (q, Val$^1$-C-4), 18.6* (q, Val$^1$-C-4), 18.41* (q, Val$^2$-C-4), 18.37 (q, Val$^1$-C-4), 18.33 (q, Val$^2$-C-4), 18.1 (s, $C(CH_3)_3$), -4.70 (q, $CH_3Si$), -4.73 (q, $CH_3Si$), -4.75* (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 642 ($[M+23]^+$, 20), 620 ($[M+1]^+$, 10), 463 (100).

**HRMS** *m/z* calcd for $C_{32}H_{53}N_3O_7Si$ 619.3653 (620.3731 for M+H), found 620.3731 (ESI).

**Cbz-MeVal-MeVal-Pro-OMe (415d)**




**415d**

**Procedure:** Using the same procedure as described for the preparation of **392a**, hydrogenolysis of **414d** (0.20 g, 0.53 mmol) followed by PyBroP (0.37 g, 0.80 mmol), DIPEA (0.18 mL, 0.14 g, 1.1 mmol) mediated coupling with Cbz-MeVal-OH (0.18 g, 0.69 mmol) gave **415d** (0.22 g, 84%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a white solid.

$[\alpha]_D$ −165 (*c* 1.4, $CH_2Cl_2$)

**IR** $\nu_{max}$ 1754, 1700, 1630 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ 7.36-7.26 (5H, m, Ph), 5.21* (1H, d, *J* = 12 Hz, HCPh), 5.16 (1H, d, *J* = 12.5 Hz, HCPh), 5.12 (1H, d, *J* = 12.5 Hz, HCPh), 5.07* (1H, d, *J* = 12 Hz, HCPh), 5.05 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 5.02* (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.72 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.47* (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.40 (1H, dd, *J* = 5.5, 8.5 Hz, Pro-HC-2), 4.35* (1H, dd, *J* = 5.5, 8.5 Hz, Pro-HC-2), 3.91-3.84 (1H, m, Pro-HC-5), 3.71-3.65 (1H, m, Pro-HC-5), 3.71 (3H, s, $H_3COC$=O), 3.70* (1H, m, $H_3COC$=O), 3.07 (3H, s, Val$^1$-$H_3CN$), 2.87* (3H, s, Val$^1$-$H_3CN$), 2.84 (, s, Val$^2$-$H_3CN$), 2.83* (3H, s, Val$^2$-$H_3CN$), 2.36-2.22 (2H, m, Val$^1$-HC-3, Val$^2$HC-3), 2.22-2.13 (1H, m, Pro-HC-3), 2.06-1.97 (1H, m, Pro-HC-4), 1.95-1.80 (2H, m, Pro-HC-3, HC-4), 0.97 (, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.96* (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.85 (, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.82* (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.83 (, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.79* (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.73 (, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.72* (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4).

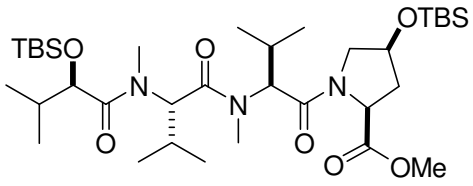
**$^{13}$C NMR** (125 MHz, $CDCl_3$) (an ca. 2.2:1 mixture of rotamers; signals for the minor rotamer indicated with an *) δ 172.7 (s, Pro-CO), 172.6* (s, Pro-CO), 171.4 (s, Val$^2$-CO),

170.8* (s, $Val^2$-CO), 169.6* (s, $Val^1$-CO), 169.4 (s, $Val^1$-CO), 157.1 (s, $NCO_2$), 156.1* (s, $NCO_2$), 136.9 (s, Ph), 136.2* (s, Ph), 128.8* (d ×2, Ph), 128.7* (d ×2, Ph), 128.63 (d ×2, Ph), 128.60* (d, Ph), 128.2 (d , Ph), 127.7 (d ×2, Ph), 68.0* (t, $CH_2Ph$), 67.6 (t, $CH_2Ph$), 61.1* (d, $Val^2$-C-2), 60.7 (d, $Val^2$-C-2), 59.37 (d, $Val^1$-C-2), 59.35* (d, $Val^1$-C-2), 59.1 (d, Pro-C-2), 52.3 (q, $CH_3OC{=}O$), 47.56* (t, Pro-C-5), 47.52 (t, Pro-C-5), 30.7 (q, $Val^1$-$CH_3N$), 30.3* (q, $Val^1$-$CH_3N$), 29.8* (q, $Val^2$-$CH_3N$), 29.40 (q, $Val^2$-$CH_3N$), 29.36 (t, Pro-C-3), 27.74* (d, $Val^1$-C-3), 27.65 (d, $Val^1$-C-3), 27.60* (d, $Val^2$-C-3), 27.5 (d, $Val^2$-C-3), 25.17 (t, Pro-C-4), 25.15* (t, Pro-C-4), 19.9* (q, $Val^1$-C-4), 19.7 (q, $Val^1$-C-4), 19.2 (q, $Val^2$-C-4), 19.0* (q, $Val^2$-C-4), 18.6* (q, $Val^2$-C-4), 18.41* (q, $Val^1$-C-4), 18.39 (q, $Val^2$-C-4), 18.33 (q, $Val^1$-C-4).

**LRMS** (EI), *m/z* (relative intensity): 489 ($[M]^+$, 1), 361 (2), 248 (11), 176 (52), 91 (100), 86 (13).

**HRMS** *m/z* calcd for $C_{26}H_{39}N_3O_6$ 489.2839, found 489.2833 (EI).

**TBS-Hmb-MeVal-MeVal-(*cis*-4-OTBS)Pro-OMe (416a)**




**416a**

**Procedure:** Using the same procedure as described for the preparation of **393a**, hydrogenolysis of **415a** (0.035 g, 0.056 mmol) followed DIPEA (0.015 mL, 0.011 g, 0.083 mmol) mediated coupling with the acid chloride prepared from **389** (0.028 g, 0.11 mmol) gave **416a** (0.033 g, 84%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick oil.

**$[\alpha]_D$** −80 (*c* 1.3, $CH_2Cl_2$)

**IR** $\nu_{max}$: 1743, 1650, 1636, 1085, 769 $cm^{-1}$.

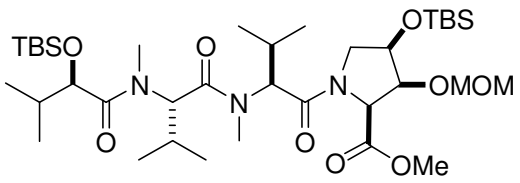
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ: 5.12 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.03 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.56 (1H, dd, *J* = 5, 9 Hz, Pro-CH-2), 4.35 (1H, dddd, *J* = 5, 5, 5, 5 Hz, Pro-HC-4), 4.14 (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 4.11 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.70 (3H, s, $H_3COC$=O), 3.53 (1H, dd, *J* = 5, 11 Hz, Pro-HC-5), 3.21 (3H, s, $H_3CN$), 3.14 (3H, s, $H_3CN$), 2.28-2.37 (2H, m, Val 1, $Val^2$-HC-3), 2.24 (1H, ddd, *J* = 5, 9, 13 Hz, Pro-HC-3), 2.08 (1H, ddd, *J* = 5, 5, 13 Hz, Pro CH-3), 1.92-2.00 (1H, m, Hmb-HC-3), 1.05 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.94 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.91 (9H, s, $(H_3C)_3C$), 0.90 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.88 (3H, d, *J* = 6.5 Hz, $Val^2$-$H_3C$-4), 0.85 (9H, s, $(H_3C)_3C$), 0.83 (3H, d, *J* = 6.5 Hz, $Val^2$-$H_3C$-4), 0.80 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.056 (3H, s, $H_3CSi$), 0.044 (3H, s, $H_3CSi$), 0.040 (3H, s, $H_3CSi$), 0.029 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.3 (s, Hmb-C- 1), 172.1 (s, $Val^2$-C- 1), 171.4 (s, $Val^1$-C- 1), 169.6 (s, Pro-CO), 79.5 (d, Hmb-C- 2), 70.6 (d, Pro-C-4), 59.0 (d, $Val^2$-C- 2), 58.5 (d, $Val^1$-C- 2), 57.2 (d, Pro-C-2), 55.2 (t, Pro-C-5), 52.1 (q, $CH_3OC$=O), 38.0 (t, Pro-C-3), 31.7 (d, Hmb-C-3), 30.9 (q, $CH_3N$), 30.0 (q, $CH_3N$), 27.61 (d, $Val^2$-C- 3), 27.58 (d, $Val^1$-C- 3), 25.8 (q, $(CH_3)_3C$), 25.6 (q, $(CH_3)_3C$), 19.4 (q, Val-C-4), 19.2 (q, Val-C-4), 18.80 (q, Val-C-4), 18.76 (q, Val-C-4), 18.6 (q, Val-C-4), 18.2 (s, $C(CH_3)_3$), 18.0 (s, $C(CH_3)_3$), 17.9 (q, Val-C-4), -4.6 (q, $CH_3Si$), -4.96 (q, $CH_3Si$), -4.94 (q, $CH_3Si$), -5.2 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):699 ($[M]^+$, 1.5), 642 (100), 328 (76), 300 (22), 187 (88), 86 (39), 73 (52).

**HRMS** *m/z* calcd for $C_{35}H_{69}N_3O_7Si_2$ 699.4674, found 699.4670.

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)Pro-OMe (416b)**




**416b**

**Procedure:** Using the same procedure as described for the preparation of **393a**, hydrogenolysis of **415b** (0.022 g, 0.032 mmol) followed by DIPEA (0.008 mL, 0.006 g, 0.049 mmol) mediated coupling with the acid chloride prepared from **389** (0.016 g, 0.065 mmol) gave **416b** (0.022 g, 90%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick oil.

**$[\alpha]_D$** −89 (*c* 1.3, $CH_2Cl_2$)

**IR**: $\nu_{max}$ 1775, 1738, 1662, 1635, 1038 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.10 (1H, d, *J* = 11 Hz, $Val^2$-HC -2), 5.04 (1H, d, *J* = 11 Hz, $Val^1$-HC- 2), 4.91 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.66 (1H, d, *J* = 7 Hz, $OCH_2O$), 4.60 (1H, d, *J* = 5.5 Hz, Pro-HC-2), 4.38-4.44 (2H, m, Pro-HC-5 & 3), 4.10 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 4.06 (1H, ddd, *J* = 4, 6.5, 10 Hz, Pro-HC-4), 3.74 (3H, s, $H_3COC$=O), 3.57 (1H, dd, *J* = 10, 10 Hz, Pro-HC-5), 3.33 (3H, s, $H_3CO$), 3.19 (3H, s, $H_3CN$), 3.15 (3H, s, $H_3CN$), 2.23-2.37 (2H, m, $Val^1$ & $Val^2$ HC-3), 1.90-2.10 (1H, m, Hmb-HC-3), 1.02 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.93 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.85-0.92 (24H, m, $(H_3C)_3C$×2, $Val^2$-$H_3C$-4, Hmb-$H_3C$-4), 0.83 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.79 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.12 (3H, s, $H_3CSi$), 0.092 (3H, s, $H_3CSi$), 0.038 (3H, s, $H_3CSi$), 0.025 (3H, s, $H_3CSi$).

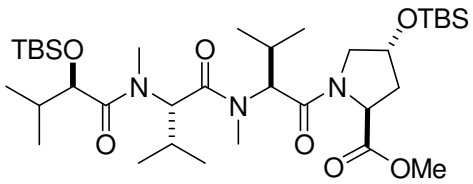
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.5 (s, Hmb-C-1), 172.3 (s, $Val^2$-C-1), 169.7 (s, $Val^1$-C-1), 167.6 (s, Pro-CO), 96.7 (t, $OCH_2O$), 79.7 (d, Hmb-C-2), 74.7 (d, Pro-C-3), 72.6 (d,

Pro-C-4), 61.4 (d, Pro-C-2), 59.0 (d, $Val^2$-C- 2), 58.8 (d, $Val^1$-C- 2), 56.1 (q, $CH_3O$), 52.2 (q, $CH_3OC=O$), 50.3 (t, Pro-C-5), 32.0 (d, Hmb-C-3), 30.9 (q, $CH_3N$), 30.2 (q, $CH_3N$), 27.9 (d, $Val^2$-C-3), 27.7 (d, $Val^1$-C-3), 26.0 (q, $(CH_3)_3C$), 25.9 (q, $(CH_3)_3C$), 19.6 (q, Val-C-4), 19.6 (q, Val-C-4), 19.02 (q, Val-C-4), 19.00 (q, Val-C-4), 18.7 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.23 (s, $C(CH_3)_3$), 18.2 (q, Val-C-4), -4.4 (q, $CH_3Si$), -4.7 (q, $CH_3Si$), -5.00 (q, $CH_3Si$), -5.04 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 782 ($[M+23]^+$, 15), 760 ($[M+1]^+$, 100), 441 (23), 328 (5).

**HRMS** *m/z* calcd for $C_{37}H_{73}N_3O_9Si_2$ 759.4885 (760.4958 for M+H), found 760.4939 (ESI).

**TBS-Hmb-MeVal-MeVal-(*trans*-4-OTBS)Pro-OMe (416c)**




**416c**

**Procedure:** Using the same procedure as described for the preparation of **393a**, hydrogenolysis of **415b** (0.30 g, 0.48 mmol) followed DIPEA (0.17 mL, 0.13 g, 0.97 mmol) mediated coupling with the acid chloride prepared from **389** (0.24 g, 97 mmol) gave **416b** (0.30 g, 88%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a thick oil.

**$[\alpha]_D$** −104 (*c* 1.0, $CH_2Cl_2$)

**IR** $\nu_{max}$: 1748, 1630, 1087, 769 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.06 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 4.99 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.42-4.48 (2H, m, Pro-HC-2, HC-4), 4.06 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.88 (1H, ddd, *J* = 2, 2, 11 Hz, Pro-HC-5), 3.76 (1H, dd, *J* = 4, 11 Hz, Pro-HC-5),

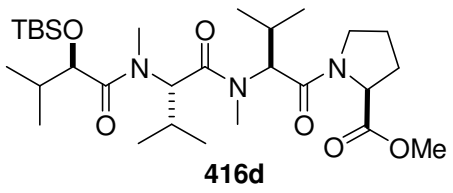
3.70 (3H, s, $H_3CO$), 3.19 (3H, s, $Val^1$-$H_3CN$), 3.10 (3H, s, $Val^2$-$H_3CN$), 2.18-2.32 (2H, m, $Val^1$-HC-3, $Val^2$-HC-3), 2.08-2.16 (1H, m, HC-3 Pro), 1.86-2.00 (2H, m, Pro-HC-3, Hmb-HC-3), 0.95 (3H, d, $J$ = 6.5 Hz, $Val^1$-$H_3C$-4), 0.89 (3H, d, $J$ = 6.5 Hz, Hmb-$H_3C$-4), 0.87 (9H, s, $(H_3C)3C$), 0.85 (3H, d, $J$ = 6.5 Hz, Hmb-$H_3C$-4), 0.79-0.84 (15 H, m, $(H_3C)3C$, $Val^2$-$H_3C$-4 ¥2), 0.74 (3H, d, $J$ = 6.5 Hz, $Val^1$-$H_3C$-4), 0.025 (3H, s, $H_3CSi$), 0.021 (3H, s, $H_3CSi$), -0.0059 (3H, s, $H_3CSi$), -0.016 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.4 (s, Hmb-CO), 172.7 (s, Pro-CO), 172.1 (s, $Val^2$-CO), 169.9 (s, $Val^1$-CO), 79.5 (d, Hmb-C-2), 71.0 (d, Pro-C-4), 59.0 (d, $Val^1$-C-2), 58.6 (d, $Val^2$-C-2), 58.1 (d, Pro-C-2), 56.0 (t, Pro-C-5), 52.3 (q, $CH_3OCO$), 38.6 (t, Pro-C-3), 31.9 (d, Hmb-C-3), 31.0 (q, $CH_3N$ Val 1), 30.2 (q, $CH_3N$ $Val^2$), 27.9 (d, $Val^2$-C-3 ), 27.7 (d, $Val^1$-C-3), 25.96 (q, $(CH_3)_3C$), 25.89 (q, $(CH_3)_3C$), 19.8 (q, $Val^2$-C-4), 19.5 (q, Hmb-C-4), 19.1 (q, $Val^2$-C-4), 18.9 (q, $Val^1$-C-4), 18.7 (q, $Val^1$-C-4), 18.4 (s, $C(CH_3)_3$), 18.14 (q, Hmb-C-4), 18.08 (s, $C(CH_3)_3$), -4.5 (q, $CH_3Si$), -4.67 (q, $CH_3Si$), -4.75 (q, $CH_3Si$), -5.1 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 700 ($[M+1]^+$, 100), 441 (6), 328 (25).

**HRMS** *m/z* calcd for $C_{35}H_{69}N_3O_7Si_2$ 699.4674 (700.4752 for M+H), found 700.4749.

**TBS-Hmb-MeVal-MeVal-Pro-OMe (416d)**




**416d**

**Procedure:** Using the same procedure as described for the preparation of **393a**, hydrogenolysis of **415d** (0.20 g, 0.41 mmol) followed by DIPEA (0.11 mL, 0.79 g, 0.61 mmol) mediated coupling with the acid chloride prepared from **389** (0.20 g, 0.82 mmol) gave **416d** (0.20 g, 85%) after fractionation of the crude by FCC (30% EtOAc in hexane) as a white solid.

**[α]$_D$** −140 (*c* 0.80, $CH_2Cl_2$)

**IR** $\nu_{max}$: 1743, 1636, 1080, 769 $cm^{-1}$.

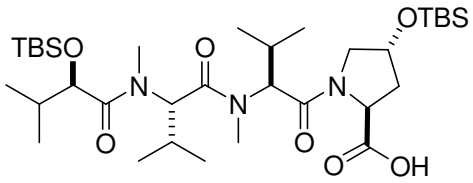
**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.13 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 5.11 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 4.43 (1H, dd, *J* = 5.5, 8 Hz, Pro-HC-2), 4.12 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.98 (1H, ddd, *J* = 6.5, 6.5, 10 Hz, Pro-HC-5), 3.75 (3H, s, $H_3COC$=O), 3.69-3.78 (1H, m, Pro-HC-5), 3.23 (3H, s, $H_3CN$), 3.17 (3H, s, $H_3CN$), 2.27-2.40 (2H, m, Val$^{1,2}$-HC-3), 2.18-2.26 (1H, m, Pro-HC-3), 2.02-2.10 (1H, m, Pro-HC-4), 1.86-2.02 (3H, m, Pro-HC-3, Pro-HC-4, Hmb-HC-3), 1.02 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.96 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.93 (9H, s, $(H_3C)_3C$), 0.92 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.90 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.86 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.81 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.06 (3H, s, $H_3CSi$), 0.05 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.5 (s, Hmb-C-1), 172.9 (s, Val$^2$-C-1), 172.3 (s, Val$^1$-C-1), 169.6 (s, Pro-CO), 79.7 (d, Hmb-C-2), 59.2 (d, Pro-C-2), 59.1 (d, Val$^1$-C-2), 58.7 (d, Val$^2$-C-2), 53.4 (q, $CH_3OC$=O), 47.6 (t, Pro-C-5), 32.0 (d, Hmb-C-3), 31.1 (q, $CH_3N$), 30.2 (q, $CH_3N$), 29.5 (t, Pro-C-3), 27.8 (d, Val$^2$-C- 3), 27.6 (d, Val$^1$-C- 3), 26.0 (q, $(CH_3)_3C$), 25.2 (t, Pro-C-4), 19.6 (q, Val$^2$-C- 4), 19.3 (q, Val$^2$-C- 4), 19.12 (q, Val$^1$-C- 4), 19.06 (q, Hmb-C-4), 18.7 (q, Val$^1$-C- 4), 18.4 (s, $C(CH_3)_3$), 18.2 (q, Hmb-C-4), -4.4 (q, $CH_3Si$), -5.0 (q, $CH_3Si$).

**LRMS** (EI), *m/z* (relative intensity):569 ([M]$^+$, 1), 512 (85), 328 (100), 300 (31), 187 (90), 128 (13), 86 (48).

**HRMS** *m/z* calcd for $C_{29}H_{55}N_3O_6Si$ 569.3860, found 569.3873.

**TBS-Hmb-MeVal-MeVal-(*trans*-4-OTBS)Pro-OH (417c)**




**417c**

**Procedure:** Trimethyltin hydroxide (0.072 g, 0.4 mmol) was added to a solution of carboxylic ester **416c** (0.028 g, 0.044 mmol) in $(CH_2Cl)_2$ (0.6 mL) and the reaction mixture was heated in an oil bath at 80 $^oC$. After 2 d, the mixture was diluted with ethyl acetate and washed with 5% HCl (aq) and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to give **417c** (0.023 g, 85%) as an oil.

**$[\alpha]_D$** −88 (*c* 0.30, $CH_3OH$)

**IR** $\nu_{max}$: 3164, 1743, 1087, 774 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.09 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.02 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.52 (1H, dd, *J* = 8, 8 Hz, Pro-HC-2), 4.48 (1H, dddd, *J* = 3, 4, 4, 4 Hz, Pro-HC-4), 4.10 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.86 (1H, br dd, *J* = 3, 11 Hz, Pro-HC-5), 3.76 (1H, dd, *J* = 4, 11 Hz, Pro-HC-5), 3.20 (3H, s, $Val^1$-$H_3CN$), 3.12 (3H, s, $Val^2$-$H_3CN$), 2.22-2.35 (2H, m, $Val^1$-HC-3, $Val^2$-HC-3), 2.19 (1H, ddd, *J* = 4, 8, 13 Hz, Pro-HC-3), 2.13 (1H, ddd, *J* = 4, 8, 13 Hz, Pro-HC-3), 1.89 (1H, m, Hmb-HC-3), 0.94 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.92 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.89 (9H, s, $(H_3C)3C$), 0.88 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.83-0.87 (15 H, m, $(H_3C)3C$, $Val^2$-$H_3C$-4 ¥2), 0.77 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.064 (3H, s, $H_3CSi$), 0.056 (3H, s, $H_3CSi$), 0.024 (3H, s, $H_3CSi$), 0.011 (3H, s, $H_3CSi$).

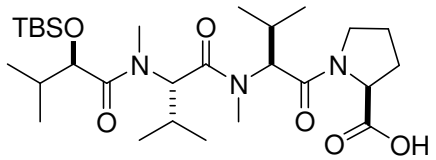
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.1 (s, Pro-CO), 173.6 (s, Hmb-CO), 172.2 (s, $Val^2$-CO), 171.0 (s, $Val^1$-CO), 79.6 (d, Hmb-C-2), 70.7 (d, Pro-C-4), 59.2 (d, $Val^1$-C-2), 58.7 (d, $Val^2$-C-2), 58.5 (d, Pro-C-2), 56.0 (t, Pro-C-5), 38.0 (t, Pro-C-3), 31.9 (d, Hmb-C-3),

31.1 (q, $Val^1$-$CH_3N$), 30.3 (q, $Val^2$-$CH_3N$), 27.9 (d, $Val^1$-C-3), 27.7 (d, $Val^2$-C-3), 26.0 (q, $(CH_3)_3C$), 25.9 (q, $(CH_3)_3C$), 19.8 (q, $Val^2$-C-4), 19.6 (q, Hmb-C-4), 19.1 (q, $Val^1$-C-4), 19.1 (q, $Val^2$-C-4), 18.7 (q, $Val^1$-C-4), 18.4 (s, $C(CH_3)_3$), 18.20 (s, $C(CH_3)_3$), 18.18 (s, Hmb-C-4), -4.4 (q, $CH_3Si$), -4.6 (q, $CH_3Si$), -4.7 (q, $CH_3Si$), -5.0 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 686 ($[M+1]^+$, 70), 441 (6), 328 (100).

**HRMS** *m/z* calcd for $C_{34}H_{67}N_3O_7Si_2$ 685.4518 (686.4590 for M+H), found 686.4620.

**TBS-Hmb-MeVal-MeVal-Pro-OH (417d)**




**417d**

**Procedure:** Aqueous LiOH (0.5 M; 0.30 mL, 0.15 mmol) was added to a stirred solution of **416d** (0.020 g, 0.035 mmol) in THF (0.5 mL) at 0 $^oC$. After 6 h, the mixture was diluted with $CH_2Cl_2$ and washed with 10% HCl (aq) to afford compound **417d** (0.018 g, 92 %) that was essentially homogeneous by NMR and was used in the next step without further purification as an oil.

**$[\alpha]_D$** −123 (*c* 0.30, $CH_3OH$)

**IR** $\nu_{max}$: 3140, 1738, 1636, 1074 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 5.12 (1H, d, *J* = 11 Hz, $Val^2$-HC -2), 5.10 (1H, d, *J* = 11 Hz, $Val^1$-HC- 2), 4.52 (1H, dd, *J* = 4, 7 Hz, Pro-HC-2), 4.11 (1H, d, *J* = 6.5 Hz, Hmb-HC -2), 3.93 (1H, ddd, *J* = 7.5, 7.5, 10.5 Hz, Pro-HC-5), 3.70 (1H, ddd, *J* = 5, 7.5, 10.5 Hz, Pro-HC-5), 3.22 (3H, s, $H_3CN$), 3.14 (3H, s, $H_3CN$), 2.25-2.40 (3H, m, Pro-HC-3, $Val^1$-HC- 3, $Val^2$-HC-3), 2.00-2.10 (2H, m, Pro-HC-3, Pro-HC-4), 1.88-2.00 (2H, m, Pro-HC-4 & Hmb-HC-3), 0.96 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.92 (3H, d, *J* = 6.5 Hz, Hmb-

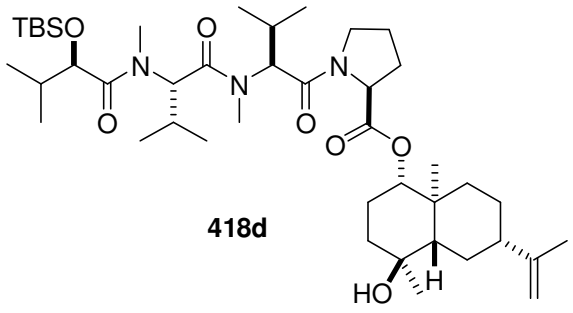
$H_3C$-4), 0.92 (9H, s, $(H_3C)_3C$), 0.89 (3H, d, $J$ = 6.5 Hz, $Val^2$-$H_3C$-4), 0.88 (3H, d, $J$ = 6.5 Hz, Hmb-$H_3C$-4), 0.85 (3H, d, $J$ = 6.5 Hz, $Val^2$-$H_3C$-4), 0.80 (3H, d, $J$ = 6.5 Hz, $Val^1$-$H_3C$-4), 0.044 (3H, s, $H_3CSi$), 0.029 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 173.7 (s, Hmb-C-1), 173.2 (s, Pro-CO), 172.5 (s, $Val^2$-C- 1), 171.8 (s, $Val^1$-C-1), 79.7 (d, Hmb-C-2), 59.9 (d, Pro-C-2), 59.4 (d, $Val^2$-C-2), 58.7 (d, $Val^1$-C-2), 48.2 (t, Pro-C-5), 32.0 (d, Hmb-C-1), 31.1 (q, $CH_3N$), 30.2 (q, $CH_3N$), 28.1 (t, Pro-C-3), 27.8 (d, $Val^2$-C-3), 27.5 (d, $Val^1$-C-3), 26.0 (q, $(CH_3)_3C$), 25.0 (t, Pro-C-4), 19.5 (q, Val-C-4), 19.3 (q, Val-C-4), 19.2 (q, Val-C-4), 19.1 (q, Val-C-4), 18.6 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.2 (q, Val-C-4), -4.4 (q, $CH_3Si$), -5.0 (q, $CH_3Si$).

**LRMS** (CI), *m/z* (relative intensity):556 ($[M+1]^+$, 1), 441 (31), 328 (89), 246 (23), 198 (39), 132 (25), 86 (27).

**HRMS** *m/z* calcd for $C_{28}H_{53}N_3O_6Si$ 555.3704 (556.3776 for M+H), found 556.3771.

**TBS-Hmb-MeVal-MeVal-Pro-Lar** (**418d**)




**418d**

**Procedure:** DCC (7.0 mg, 0.032 mmol) was added to a stirred solution of **417d** (18 mg, 0.032 mmol), laidinol A (**51**) (7.0 mg, 0.028 mmol), and DMAP (0.5 mg, 0.032 mmol) in $CH_2Cl_2$ (0.5 mL) at 0 °C. After 1 h, the mixture was allowed to warm to ambient temperature and after 20 h, was diluted with ethyl acetate. The precipitated DCU was filtered off and the combined filtrate and ethyl acetate washings were washed sequentially with aqueous citric acid (0.5 M) and saturated aqueous $NaHCO_3$, dried over

$Na_2SO_4$, concentrated, and fractionated by PTLC (60% ethyl acetate in hexane) to give compound **418d** (23 mg, 85% over 2 steps from **413d**) as an oil.

**$[\alpha]_D$** −90 (*c* 0.71, $CH_2Cl_2$)

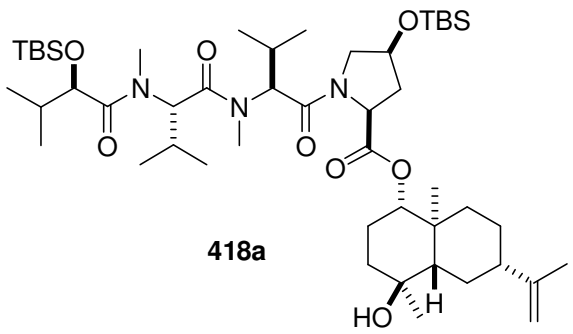
**IR** $\nu_{max}$ 3478, 3079, 1760, 1640 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.12 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.09 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.70 (2H, br s, Lar-$H_2C$-12), 4.62 (1H, dd, *J* = 4.5, 12 Hz, Lar-HC-1), 4.43 (1H, dd, *J* = 5, 8.5 Hz, Pro-HC-2), 4.11 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.92 (1H, ddd, *J* = 6.5, 6.5, 10 Hz, Pro-HC-5), 3.70 (1H, ddd, *J* = 6.5, 6.5, 10 Hz, Pro-HC-5), 3.20 (3H, s, $Val^1$-$H_3CN$), 3.13 (3H, s, $Val^2$-$H_3CN$), 2.38-2.25 (2H, m, $Val^1$-HC-3, $Val^2$-HC-3), 2.25-2.15 (1H, m, Pro-HC-3), 2.26-180 (8H, , Lar-HC-2, HC-3, HC-6, HC-7; Pro-HC-3, $H_2C$-4; Hmb-HC-3), 1.74 (3H, s, Lar-$H_3C$-13), 1.72-1.62 (2H, m, Lar-HC-2, HO), 1.61-1.52 (3H, m, Lar-HC-3, HC-8, HC-9), 1.40-1.17 (4H, m, Lar-HC-5, HC-6, HC-8, HC-9) , 1.14 (3H, s, Lar-$H_3C$-14), 1.02 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.96 (3H, s, Lar-$H_3C$-15), 0.93 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.91 (9H, s, $(H_3C)_3C$), 0.90 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.87 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.84 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.79 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 0.04 (3H, s, $H_3CSi$), 0.03 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.5 (s, Hmb-CO), 172.1 (s, $Val^2$-CO), 171.9 (s, Pro-CO), 169.5 (s, $Val^1$-CO), 150.4 (s, Lar-C-11), 108.6 (t, Lar-C-12), 81.8 (d, Lar-C-1), 79.5 (d, Hmb-C-2), 71.5 (s, Lar-C-4), 59.3 (d, Pro-C-2), 59.2 (d, $Val^1$-C-2), 58.7 (d, $Val^2$-C-2), 53.4 (d, Lar-C-5), 47.6 (t, Pro-C-5), 45.7 (d, Lar-C-7), 40.8 (t, Lar-C-3), 40.6 (t, Lar-C-9), 38.5 (s, Lar-C-10), 32.0 (d, Hmb-C-3), 31.1 (q, $Val^1$-$CH_3N$), 30.2 (q, $Val^2$-$CH_3N$), 29.7 (t, Pro-C-3), 27.8 (d, $Val^1$-C-3), 27.5 (d, $Val^2$-C-3), 26.5 (t, Lar-C-8), 26.0 (q ×3, $(CH_3)_3C$), 25.9 (t, Lar-C-6), 25.4 (t, Lar-C-2), 25.1 (t, Pro-C-4), 23.0 (q, Lar-C-14), 21.3 (q, Lar-C-13), 19.6 (q, Hmb-C-4), 19.38 (q, Val-C-4), !9.36 (q, Val-C-4), 19.0 (q, Val-C-4), 18.7 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.1 (q, Hmb-C-4), 14.3 (q, Lar-C-15), -4.4 (q, $CH_3Si$), -5.0 (q, $CH_3Si$).

**HRMS** *m/z* calcd for $C_{43}H_{77}N_3O_7Si$ 775.5531 (798.5428 for M+Na), found 798.5421 (ESI).

**TBS-Hmb-MeVal-MeVal-(*cis*-4-OTBS)Pro-Lar (418a):**




**418a**

**Procedure:** Using the same procedure as described for the preparation of **418d**, DCC (0.0040 g, 0.019 mmol), DMAP (0.2 mg, 0.0019 mmol) mediated esterification of **417a** (0.012 g, 0.017 mmol, prepared from hydrolysis of 414c using Me3SnOH) with lairdinol A (**51**) (0.0045 g, 0.019 mmol) gave **418a** (0.014 g, 88%) after fractionation of the crude by FCC (40% EtOAc in hexane) as an oil.

$[\alpha]_D$ −73 (*c* 0.63, $CH_2Cl_2$)

**IR** $\nu_{max}$ 3471, 3072, 1759, 1635 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.12 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 5.02 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.71 (2H, br s, Lar-$H_2$C-12), 4.61 (1H, dd, *J* = 4, 11.5 Hz, Lar-HC-1), 4.47 (1H, dd, *J* = 5.5, 9 Hz, Pro-HC-2), 4.32 (1H, dddd, *J* = 5.5, 5.5, 10.5, 10.5 Hz, Pro-HC-4), 4.20 (1H, dd, *J* = 5.5, 10.5 Hz, Pro-HC-5), 4.11 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.49 (1H, dd, *J* = 5.5, 10.5 Hz, Pro-HC-5), 3.21 (3H, s, $H_3$CN), 3.14 (3H, s, $H_3$CN), 2.37-2.25 (3H, m, Pro-HC-3, Val$^1$-HC-3, Val$^2$-HC-3), 2.01 (1H, ddd, *J* = 5.5, 5.5, 10.5 Hz, Pro-HC-3), 1.99-1.91 (2H, m, Hmb-HC-3, Lar-HC-7), 1.84-1.91 (1H, m, Lar-HC-2), 1.81 (1H, ddd, *J* = 3, 3, 12.5 Hz, Lar-HC-3), 1.74 (3H, s, Lar-$H_3$C-13), 1.52-1.62 (4H, m, Lar-HC-2, HC-3, HC-6, HC-8, HC-9), 1.32-1.40 (2H, m, Lar-HC-6, HC-8), 1.19-1.29 (1H, m, Lar-HC-5), 1.12-1.18 (1H, m, Lar-HC-9), 1.14 (1H, s, Lar-$H_3$C-14), 1.06 (3H, d, *J* = 6.5 Hz, Val-$H_3$C-4), 0.95 (3H, s, Lar-$H_3$C-15), 0.93 (3H, d, *J* = 6.5 Hz, Hmb-$H_3$C-4), 0.91 (9H, s, $(H_3C)_3$C), 0.90 (3H, d, *J* = 6.5 Hz, Val- or Hmb-$H_3$C-4), 0.88 (3H, d, *J* = 6.5 Hz, Hmb- or Val-$H_3$C-4), 0.87 (9H, s, $(H_3C)_3$C), 0.83 (3H, d, *J* = 6.5 Hz, Val-$H_3$C-4),

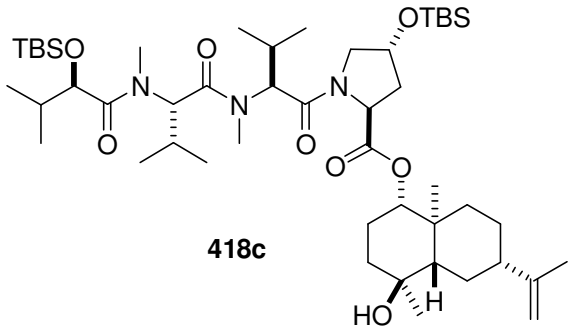
0.79 (3H, d, $J$ = 6.5 Hz, Val-$H_3C$-4), 0.07 (3H, s, $H_3CSi$), 0.05 (3H, s, $H_3CSi$), 0.04 (3H, s, $H_3CSi$), 0.02 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.5 (s, Hmb-CO), 172.2 (s, Pro-CO), 170.7 (s, Val$^2$-CO), 169.7 (s, Val$^1$-CO), 150.4 (s, Lar-C-11), 108.6 (t, Lar-C-12), 81.8 (d, Lar-C-1), 79.6 (d, Hmb-C-2), 71.6 (s, Lar-C-4), 70.7 (d, Pro-C-4), 59.2 (d, Val$^1$-C-2), 58.6 (d, Val$^2$-C-2), 57.5 (d, Pro-C-2), 55.1 (t, Pro-C-5), 53.4 (d, Lar-C-5), 45.7 (d, Lar-C-7), 40.8 (t, Lar-C-3), 40.7 (t, Lar-C-9), 38.5 (s, Lar-C-10), 38.0 (t, Pro-C-3), 31.9 (d, Hmb-C-3), 31.2 (q, $CH_3N$), 30.2 (q, $CH_3N$), 27.8 (d, Val$^2$-C-3), 27.7 (d, Val$^1$-C-3), 26.4 (t, Lar-C-8), 26.0 (q, $(CH_3)_3C$), 25.9 (q, $(CH_3)_3C$), 25.8 (t, Lar-C-6), 25.4 (t, Lar-C-2), 23.0 (q, Lar-C-14), 21.3 (q, Lar-C-13), 19.6 (q, Val- or Hmb-C-4), 19.5 (q, Hmb- or Val-C-4), 19.3 (q, Val-C-4), 19.0 (q, Val-C-4), 18.8 (q, Val-C-4), 18.4 (s, $C(CH_3)_3$), 18.2 (s, $C(CH_3)_3$), 18.1 (q, Hmb-C-4), 14.3 (q, Lar-C-15), -4.4 (q, $CH_3Si$), -4.6 (q, $CH_3Si$), -4.7 (q, $CH_3Si$), -5.0 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 906 ([M+1]$^+$, 100), 441 (5), 399 (4), 328 (10), 225 (15).

**HRMS** *m/z* calcd for $C_{49}H_{91}N_3O_8Si_2$ 905.6345 (906.6423 for M+H), found 906.6385 (ESI).

**TBS-Hmb-MeVal-MeVal-(*trans*-4-OTBS)Pro-Lar (418c):**




**418c**

**Procedure:** Using the same procedure as described for the preparation of **418d**, DCC (0.0090 g, 0.044 mmol), DMAP (0.5 mg, 0.0029 mmol) mediated esterification of **417c** (0.020 g, 0.029 mmol) with lairdinol A (**51**) (0.006 g, 0.026 mmol) gave **418c** (0.022 g, 85%) after fractionation of the crude by FCC (30% EtOAc in hexane) as an oil.

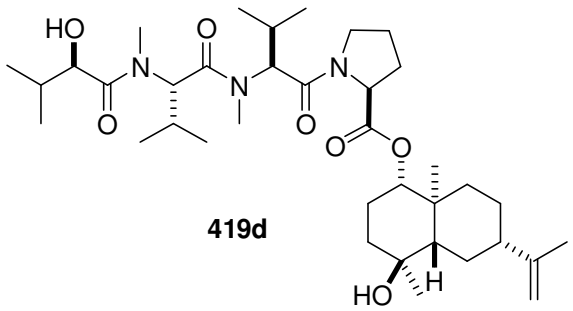
**$[\alpha]_D$** −67 (*c* 0.40, $CH_2Cl_2$)

**IR** $\nu_{max}$ 3320, 3024, 1738, 1625 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.11 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.03 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.70 (2H, br s, Lar-$H_2$C-12), 4.63 (1H, dd, *J* = 4, 11.5 Hz, Lar-HC-1), 4.50-4.45 (2H, m, Pro-HC-2, Pro-HC-4), 4.11 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 3.81 (1H, dd, *J* = 4.5, 11 Hz, Pro-HC-5), 3.78 (1H, dd, *J* = 2.5, 11 Hz, Pro-HC-5), 3.18 (3H, s, $Val^1$-$H_3$CN), 3.10 (3H, s, $Val^2$-$H_3$CN), 2.36-2.22 (2H, m, $Val^1$-HC-3, $Val^2$-HC-3), 2.11 (1H, ddd, *J* = 4, 8, 12.5 Hz, Pro-HC-3), 2.05-1.96 (1H, m, Pro-HC-3), 1.96-1.78 (3H, m, Hmb-HC-3, Lar-HC-2, Lar-HC-7), 1.73 (3H, s, Lar-$H_3$C-13), 1.72-1.66 (1H, m, Lar-HC-3), 1.62-1.49 (5H, m, Lar-HC-2, HC-3, HC-6, HC-8, HC-9), 1.39-1.29 (2H, m, Lar-HC-6, HC-9), 1.29-1.22 (1H, m, Lar-HC-5), 1.21-1.15 (1H, m, Lar-HC-9), 1.14 (3H, s, Lar-$H_3$C-14), 1.00 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3$C-4), 0.96 (3H, s, Lar-$H_3$C-15), 0.92 (3H, d, *J* = 6.5 Hz, Hmb-$H_3$C-4), 0.90 (9H, s, $(H_3C)_3C$), 0.89 (3H, d, *J* = 6.5 Hz, Hmb-$H_3$C-4), 0.83-0.87 (15H, m, (H3C)3C, $Val^2$-$H_3$C-4, $Val^2$-$H_3$C-4), 0.77 (3H, d, *J* = 6.5 Hz, $Val^1$-HC-4), 0.055 (3H, s, $H_3$CSi), 0.045 (3H, s, $H_3$CSi), 0.023 (3H, s, $H_3$CSi), 0.012 (3H, s, $H_3$CSi).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.4 (s, Hmb-CO), 172.1 (s, Pro-CO), 171.9 (s, $Val^2$-CO), 169.7 (s, $Val^1$-CO), 150.3 (s, Lar-C-11), 108.7 (t, Lar-C-12), 81.8 (d, Lar-C-1), 79.4 (d, Hmb-C-2), 71.5 (s, Lar-C-4), 70.8 (d, Pro-C-4), 59.2 (d, $Val^1$-C-2), 58.7 (d, $Val^2$-C-2), 58.3 (d, Pro-C-2), 55.7 (t, Pro-C-5), 53.4 (d, Lar-C-5), 45.7 (d, Lar-C-7), 40.8 (t, Lar-C-3), 40.6 (t, Lar-C-9), 38.7 (s, Lar-C-10), 38.5 (t, Pro-C-3), 31.9 (d, Hmb-C-3), 31.1 (q, $Val^1$-$CH_3$N), 30.2 (q, $Val^2$-$CH_3$N), 27.9 (d, $Val^1$-C-3), 27.6 (d, $Val^2$-C-3), 26.4 (t, Lar-C-8), 26.01 (q, $(CH_3)_3$C), 25.97 (q, $(CH_3)_3$C), 25.8 (t, Lar-C-6), 25.2 (t, Lar-C-2), 23.0 (q, Lar-C-14), 21.2 (q, Lar-C-13), 19.9 (q, $Val^2$-C-4), 19.7 (q, Hmb-C-4), 19.3 (q, $Val^1$-C-4), 19.0 (q, $Val^2$-C-4), 18.7 (q, $Val^1$-C-4) , 18.4 (s, C($CH_3$)3), 18.2 (s, C($CH_3$)3), 18.0 (q, Hmb-C-4), 14.3 (q, Lar-C-15), -4.4 (q, $CH_3$Si), -4.6 (q, $CH_3$Si), -4.7 (q, $CH_3$Si), -5.0 (q, $CH_3$Si).

**Hmb-MeVal-MeVal-Pro-Lar (419d):**



**419d**

**Procedure:** A solution of TBAF (50 mg, 0.19 mmol) in $CH_2Cl_2$ (0.1 mL) was added to a stirred solution of **418d** (15 mg, 0.019 mmol) in $CH_2Cl_2$ (0.1 mL) at room temperature. After 3 d, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $Na_2SO_4$ and fractionated by PTLC (5% MeOH in $CH_2Cl_2$) to afford compound **419d** (12 mg, 92%) as an oil.

**$[\alpha]_D$** −149 (*c* 0.65, $CH_2Cl_2$)

**IR** $\nu_{max}$ 3454, 3080, 1738, 1624 $cm^{-1}$.

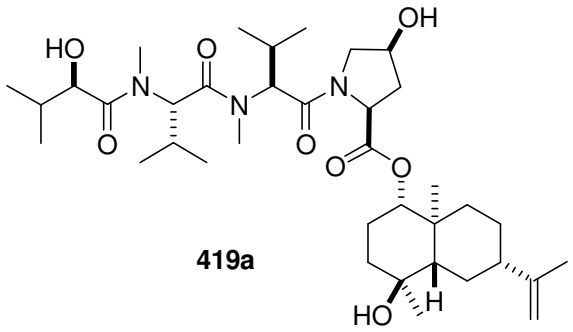
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.15 (1H, d, *J* = 11 Hz, Val$^2$-HC-2 ), 5.06 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.71 (2H, br s, Lar-$H_2$C-12), 4.62 (1H, dd, *J* = 4, 11.5 Hz, Lar-HC-1), 4.43 (1H, dd, *J* = 5, 8.5 Hz, Pro-HC-2), 4.26 (1H, br s, Hmb-HC-2), 3.88 (1H, ddd, *J* = 6.5, 6.5, 10 Hz, Pro-HC-5), 3.71 (1H, ddd, *J* = 6.5, 6.5, 10 Hz, Pro-HC-5), 3.45 (1H, br s, HO), 3.16 (3H, s, $H_3$CN), 3.00 (3H, s, $H_3$CN), 2.40-2.25 (2H, m, Val$^1$-HC-3, Val$^2$-HC-3), 2.25-2.15 (1H, m, Pro-HC-3), 2.07-199 (1H, m, Pro-HC-4), 1.98-1.78 (7H, m, Lar-HC-2, HC-3, HC-6, HC-7; Pro-HC-3, HC-4; Hmb-HC-3), 1.74 (3H, s, Lar-$H_3$C-13), 1.74-1.65 (1H, m, Lar-HC-2), 1.62-1.53 (3H, m, Lar-HC-3, HC-8, HC-9), 1.40-1.16 (4H, m, Lar-HC-5, HC-6, HC-8, HC-9), 1.15 (3H, s, Lar-$H_3$C-14), 1.10 (3H, d, *J* = 6.5 Hz, Hmb-$H_3$C-4), 1.03 (3H, d, *J* = 6.5 Hz, Val-$H_3$C-3), 0.97 (3H, s, Lar-$H_3$C-15), 0.88 (3H, d, *J* = 7 Hz, Val-$H_3$C-3), 0.86 (3H, d, *J* = 7 Hz, Val-$H_3$C-3), 0.81 (3H, d, *J* = 6.5 Hz, Hmb-$H_3$C-4), 0.76 (3H, d, *J* = 6.5 Hz, Val-$H_3$C-3).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.0 (s, Hmb-CO), 171.9 (s, Pro-CO), 171.0 (s, $Val^2$-CO), 169.3 (s, $Val^1$-CO), 150.4 (s, Lar-C-11), 108.7 (t, Lar-C-12), 81.8 (d, Lar-C-1), 72.9 (d, Hmb-C-2), 71.5 (s, Lar-C-4), 59.7 (d, $Val^1$-C-2), 59.31 (d, Pro-C-2), 59.26 (d, $Val^2$-C-2), 53.4 (d, Lar-C-5), 47.5 (t, Pro-C-5), 45.7 (d, Lar-C-7), 40.8 (t, Lar-C-3), 40.6 (t, Lar-C-9), 38.5 (s, Lar-C-10), 31.0 (d, Hmb-C-3), 30.8 (q, $CH_3N$), 30.1 (q, $CH_3N$), 29.7 (t, Pro-C-3), 27.7 (d, $Val^1$-C-3), 27.6 (d, $Val^2$-C-3), 26.4 (t, Lar-C-8), 25.8 (t, Lar-C-6), 25.4 (t, Lar-C-2), 25.1 (t, Pro-C-4), 23.0 (q, Hmb-C-4), 21.3 (q, Lar-C-13), 20.3 (q, Lar-C-14), 19.6 (q, Val-C-4), 19.4 (q, Val-C-4), 18.6 (q, Val-C-4), 18.5 (q, Val-C-4), 14.7 (q, Hmb-C-4), 14.3 (q, Lar-C-15).

**LRMS** (EI), *m/z* (relative intensity): 661 ($[M]^+$, 1), 327 (13), 214 (100), 197 (5), 186 (23), 86 (33).

**HRMS** *m/z* calcd for $C_{37}H_{63}N_3O_7$ 661.4666, found 661.4664 (EI).

**Hmb-MeVal-MeVal-(*cis*-4-OH)Pro-Lar (419a):**




**419a**

**Procedure:** Using the same procedure as described for the preparation of **419d**, TBAF (0.029 g, 0.11 mmol) deprotection of **418a** (0.010 g, 0.011 mmol) gave **419a** (0.007 g, 95%) after fractionation of the crude by FCC (60% EtOAc in hexane) as an oil.

**$[\alpha]_D$** −80 (*c* 0.70, $CH_2Cl_2$)

**IR** $\nu_{max}$ 3442, 3070, 1744, 1630 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.15 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.06 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.71 (2H, br s, Lar-$H_2$C-12), 4.67 (1H, dd, *J* = 4, 11 Hz, Lar-HC-1), 4.47

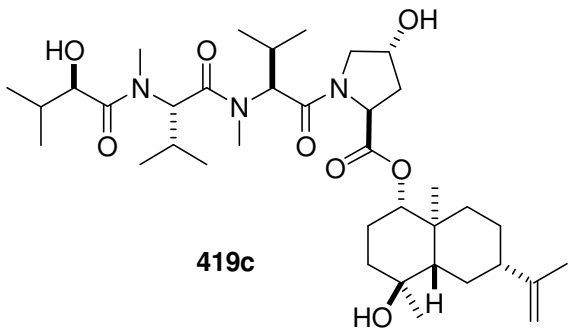
(1H, dd, *J* = 1.5, 10 Hz, Pro-HC-2), 4.40 (1H, br s, Pro-HC-4), 4.26 (1H, br d, *J* = 3.5 Hz, Hmb-HC-2), 3.93 (1H, dd, *J* = 1.5, 12 Hz, Pro-HC-5), 3.83 (1H, dd, *J* = 4, 12 Hz, Pro-HC-5), 3.45 (1H, br s, HO), 3.41 (1H, br s, HO), 3.13 (3H, s, $H_3CN$), 2.96 (3H, s, $H_3CN$), 2.40-2.25 (3H, m, Pro-HC-3, $Val^1$-HC3, $Val^2$-HC-3), 2.10 (1H, d, *J* = 13 Hz, Pro-HC-3), 1.98-1.80 (7H, m, Lar-$H_2C$-2, HC-3, HC-6, HC-7, HC-9, Hmb-C-3) , 1.75 (3H, s, Lar-$H_3C$-13), 1.65-1.55 (2H, m, Lar-HC-3, HC-8), 1.42-1.33 (2H, m, Lar-HC-5, HC-8), 1.32-1.21 (2H, m, Lar-HC-6, HC-9), 1.16 (3H, s, Lar-$H_3C$-14), 1.10 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 1.02 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4), 1.01 (3H, s, Lar-$H_3C$-15), 0.87 (3H, d, *J* = 7 Hz, Val-$H_3C$-4), 0.86 (3H, d, *J* = 7 Hz, Val-$H_3C$-4), 0.81 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.78 (3H, d, *J* = 6.5 Hz, Val-$H_3C$-4).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 174.9 (s, Hmb-CO), 174.6 (s, Pro-CO), 171.0 (s, $Val^2$-CO), 170.1 (s, $Val^1$-CO), 150.3 (s, Lar-C-11), 108.7 (t, Lar-C-12), 83.1 (d, Lar-C-1), 72.8 (d, Hmb-C-2), 71.55 (d, Pro-C-4), 71.49 (s, Lar-C-4), 59.6 (d , $Val^1$-C-2), 59.3 (d, $Val^2$-C-2), 58.5 (s, Pro-C-2), 56.9 (t, Pro-C-5), 53.4 (d, Lar-C-5), 45.6 (d, Lar-C-7), 40.7 (t, Lar-C-3), 40.6 (t, Lar-C-9), 38.5 (s, Lar-C-10), 37.2 (t, Pro-C-3), 31.0 (d, $CH_3N$), 30.8 (q, Hmb-C-3), 30.1 (q, $CH_3N$), 27.7 (d, $Val^1$-C-3), 27.5 (d, $Val^2$-C-3), 26.4 (t, Lar-C-8), 25.8 (t, Lar-C-6), 25.3 (t, Lar-C-2), 23.0 (q, Lar-C-14), 21.3 (q, Lar-C-13), 20.3 (q, Hmb-C-4), 19.8 (q, Val-C-4), 19.3 (q, Val-C-4), 18.6 (q, Val-C-4), 18.5 (q, Val-C-4), 14.7 (q, Hmb-C-4), 14.4 (q, Lar-C-15).

**LRMS** (EI), *m/z* (relative intensity): 677 ($[M]^+$, 1), 327 (28), 214 (100), 186 (34), 124 (20), 86 (60).

**HRMS** *m/z* calcd for $C_{37}H_{63}N_3O_8$ 677.4615, found 677.4611 (EI).

**Hmb-MeVal-MeVal-(*trans*-4-OH)Pro-Lar (419c):**



**419c**

**Procedure:** Using the same procedure as described for the preparation of **419d**, TBAF (0.046 g, 0.18 mmol) deprotection of **418c** (0.016 g, 0.018 mmol) gave **419c** (0.011 g, 91%) after fractionation of the crude by FCC (60% EtOAc in hexane) as an oil.

$[\alpha]_D$ −137 (*c* 0.40, $CH_2Cl_2$)

**IR** (DRIFT) $\nu_{max}$ 3400, 3072, 1713, 1630 $cm^{-1}$.

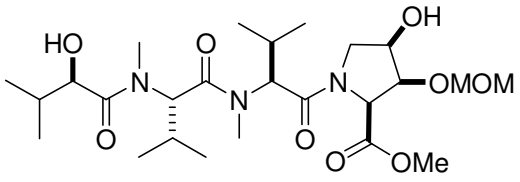
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.13 (1H, d, *J* = 11 Hz, Val$^2$-HC-2) , 4.84 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.70 (2H, br s, Lar-$H_2$C-2) , 4.61 (1H, dd, *J* = 4, 12 Hz, Lar-HC-1), 4.57 (1H, dd, *J* = 8, 8 Hz, Pro-HC-2), 4.50 (1H, m, Pro-HC-4), 4.30-4.23 (2H, m, Pro-HC-5, Hmb-HC-2), 3.48 (1H, br s, OH) , 3.21 (3H, s, Val$^1$-$H_3$CN), 2.98 (3H, s, Val$^2$-$H_3$CN), 2.37-2.25 (3H, m, Val$^1$-HC-3, Val$^2$-HC-3, Pro-HC-3), 1.98 (1H, ddd, *J* = 4, 8, 13 Hz, Pro-HC-3), 1.95-1.78 (5H, m, Lar-HC-2, HC-3, HC-6, HC-7; Hmb-HC-3), 1.75-1.65 (3H, s), 1.73 (3H, s, Lar-$H_3$C-13), 1.63-1.51 (3H, m, Lar-HC-3, HC-8, HC-9), 1.40-1.20 (4H, m, Lar-HC-5, HC-6, HC-8, HC-9), 1.14 (3H, s, Lar-$H_3$C-14), 1.09 (3H, d, *J* = 7 Hz, Hmb-$H_3$C-4), 1.01 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 0.95 (3H, s, Lar-$H_3$C-15), 0.86 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.84 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.80 (3H, d, *J* = 7 Hz, Hmb-$H_3$C-4), 0.78 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.0 (s, Hmb-CO), 172.05 (s, Pro-CO), 171.92 (s, Val$^2$-CO), 169.8 (s, Val$^1$-CO), 150.3 (s, Lar-C-11), 108.7 (t, Lar-C-12) , 82.0 (d, Lar-C-1) , 72.9 (d, Hmb-C-2), 71.5 (s, Lar-C-4), 70.5 (d, Pro-C-4), 60.2 (d, Val$^1$-C-2), 59.2 (d, Val$^2$-C-2), 57.8 (d, Pro-C-2), 55.8 (t, Pro-C-5), 53.4 (d, Lar-C-5), 45.7 (d, Lar-C-7), 40.8 (t,

Lar-C-3), 40.6 (t, Lar-C-9), 38.5 (s, Lar-C-10), 38.1 (t, Pro-C-3), 31.3 (q, Val$^1$-$CH_3N$), 30.9 (d, Hmb-C-3), 30.1 (q, Val$^2$-$CH_3N$), 27.8 (d, Val$^1$-C-3), 27.7 (d, Val$^2$-C-3), 25.8 (t, Lar-C-2), 25.4 (t, Lar-C-6), 25.2 (t, Lar-C-8), 23.0 (q, Lar-C-14), 21.3 (q, Lar-C-13), 20.3 (q, Hmb-C-4), 19.5 (q, Val-C-4), 19.3 (q, Val-C-4) , 18.9 (q, Val-C-4), 18.7 (q, Val-C-4), 14.7 (q, Hmb-C-4), 14.3 (q, Lar-C-15).

**HRMS** *m/z* calcd. for $C_{37}H_{63}N_3O_8$: 677.4615 (678.4687 for M+H); found: 678.4698 (ESI).

**Hmb-MeVal-MeVal-(4-OH)(3-OMOM)Pro-OMe (420)**:




**420**

**Procedure:** TBAF (0.085 g, 0.33 mmol) was added to a stirred solution of **416b** (0.025 g, 0.033 mmol) in $CH_2Cl_2$ (0.1 mL) at room temperature. After 2 d, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated using FCC (10% MeOH in $CH_2Cl_2$) to afford compound **420** (0.016 mg, 90%) as an oil.

**$[\alpha]_D$** −139 (*c* 0.67, $CH_2Cl_2$)

**IR** $\nu_{max}$ 3417, 1727, 1630 cm$^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.12 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 5.01 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.73 (1H, d, *J* = 7 Hz, $H_2CO_2$), 4.70 (1H, d, *J* = 7 Hz, $H_2CO_2$), 4.60 (1H, d, *J* = 8 Hz, Pro-HC-2), 4.37 (1H, dd, *J* = 4, 8 Hz, Pro-HC-3), 4.28-4.21 (2H, br s, Pro-HC-4, Hmb-HC-2), 3.94 (1H, dd, *J* = 4, 12 Hz, Pro-HC-5), 3.89 (1H, dd, *J* = 3, 12 Hz, Pro-HC-5), 3.79 (3H, s, $H_3COCO$), 3.42 (3H, s, $H_3CO$), 3.12 (3H, s, Val$^1$-$H_3CN$), 2.96 (3H, s, Val$^2$-$H_3CN$), 2.33 (1H, dqq, *J* = 11, 6.5, 6.5 Hz, Val$^2$-HC-3), 2.27 (1H, dqq, *J* =

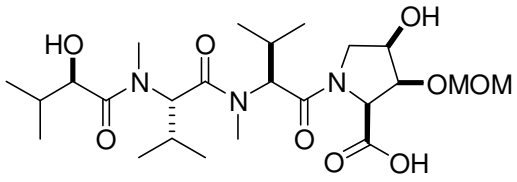
11, 6.5, 6.5 Hz, Val$^1$-HC-3), 1.90 (1H, dqq, *J* = 2, 7, 7 Hz, Hmb-HC-3), 1.08 (3H, d, *J* = 67 Hz, Hmb-$H_3$C-4), 0.98 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4), 0.85 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.84 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3$C-4), 0.79 (3H, d, *J* = 7 Hz, Hmb-$H_3$C-4), 0.76 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3$C-4).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.0 (s, Hmb-CO), 171.3 (s, Pro-CO), 171.2 (s, Val$^2$-CO), 170.4 (s, Val$^1$-CO), 96.6 (t, $CH_2O2$), 75.8 (d, Pro-C-3), 72.8 (d, Hmb-C-2 ), 71.2 (d, Pro-C-4), 60.8 (d, Pro-C-2), 59.3 (d, Val$^2$-C-2), 58.8 (d, Val$^1$-C-2), 54.4 (q, $CH_3O$), 53.8 (t, Pro-C-5), 52.9 (q, $CH_3OCO$), 30.9 (d, Hmb-C-3), 30.8 (q, Val$^1$-$CH_3N$), 30.1 (q, Val$^2$-$CH_3N$), 27.8 (d, Val$^1$-C-3), 27.5 (d, Val$^2$-C-3), 20.3 (q, Hmb-C-4), 19.7 (q, Val$^2$-C-4), 19.1 (q, Val$^1$-C-4), 18.7 (q, Val$^1$-C-4), 18.6 (q, Val$^2$-C-4), 14.7 (q, Hmb-C-4).

**LRMS** (ESI), *m/z* (relative intensity): 554 ([M+23]$^+$, 12), 532 ([M+1]$^+$, 23), 327 (100).

**HRMS** *m/z* calcd for $C_{25}H_{45}N_3O_9$ 531.3156 (532.3228 for M+H), found 532.3237 (ESI).

**Hmb-MeVal-MeVal-(4-OH)(3-OMOM)Pro (421)**:




**421**

**Procedure:** Trimethyltin hydroxide (0.031 g, 0.17 mmol) was added to a solution of carboxylic ester **420** (9.0 mg, 0.017 mmol) in $(CH_2Cl)_2$ (0.5 mL) and the reaction mixture was heated in an oil bath at 80 $^oC$. After 2 d, the mixture was diluted with ethyl acetate and washed with 5% HCl (aq.) and brine. The organic layer was dried over $Na_2SO_4$, concentrated, and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to give **421** (7.5 g, 85%) as an oil.

**$[\alpha]_D$** −106 (*c* 0.85, $CH_3OH$)

**IR** $\nu_{max}$ 3422, 3175, 1727, 1635 cm$^{-1}$.

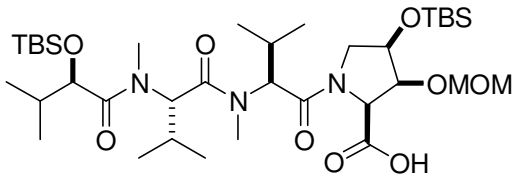
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.13 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.00 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.77 (1H, d, *J* = 6.5 Hz, $OCH_2O$), 4.74 (1H, d, *J* = 6.5 Hz, $OCH_2O$), 4.63 (1H, d, *J* = 8 Hz, Pro-HC-2), 4.41 (1H, dd, *J* = 4, 8 Hz, HC-3 Pro), 4.24-4.29 (2H, m, Pro-HC-4, Hmb-HC-2), 3.95 (1H, dd, *J* = 4.5 11.5 Hz, Pro-HC-5), 3.87 (1H, dd, *J* = 3, 11.5 Hz, Pro-HC-5), 3.43 (3H, s, $H_3CO$), 3.12 (3H, s, $Val^1$-$H_3CN$), 2.97 (3H, s, $Val^2$-$H_3CN$), 2.38-2.31 (1H, m, $Val^2$-HC-3), 2.32-2.24 (1H, m, $Val^1$-HC-3), 1.87-1.95 (1H, dqq, *J* = 2, 7, 7 Hz, Hmb-HC-3), 1.08 (3H, d, *J* = 7 Hz, Hmb-$H_3C$-4), 0.97 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4), 0.86 (3H, d, *J* = 6.5 Hz, $Val^2$-$H_3C$-4), 0.84 (3H, d, *J* = 6.5 Hz, $Val^2$-$H_3C$-4), 0.81 (3H, d, *J* = 7 Hz, Hmb-$H_3C$-4), 0.76 (3H, d, *J* = 6.5 Hz, $Val^1$-$H_3C$-4).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.0 (s, Hmb-CO), 172.5 (s, Pro-CO), 171.3 (s, $Val^2$-CO), 170.5 (s, $Val^1$-CO), 96.8 (t, $OCH_2O$), 75.9 (d, Pro-C-3), 72.9 (d, Hmb-C-2), 71.2 (d, Pro-C-4), 60.8 (d, Pro-C-2), 59.3 (d, $Val^2$-C-2), 59.0 (d, $Val^1$-C-2), 56.5 (q, $CH_3O$), 53.4 (t, Pro-C-5), 31.0 (d, Hmb-C-3), 30.9 (q, $Val^1$-$CH_3N$), 30.2 (q, $Val^2$-$CH_3N$), 27.8 (d, $Val^1$-C-3), 27.5 (d, $Val^2$-C-3), 20.2 (q, Hmb-C-4), 19.7 (q, $Val^2$-C-4), 19.2 (q, $Val^1$-C-4), 18.7 (q, $Val^1$-C-4), 18.6 (q, $Val^2$-C-4), 14.9 (q, Hmb-C-4).

**LRMS** (ESI), *m/z* (relative intensity): 518 ($[M+1]^+$, 10), 327 (100), 212 (4).

**HRMS** *m/z* calcd for $C_{24}H_{43}N_3O_9$ 517.2999 (518.3072 for M+H), found 518.3093.

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)Pro (422)**:




**422**

**Procedure:** 2,6-Lutidine (0.022 mL, 0.021 g, 0.19 mmol) and TBSOTf (0.031 mL, 0.036 g, 0.13 mmol) were sequentially added to a stirred solution of **421** (0.010 g, 0.019 mmol) in dry $CH_2Cl_2$ (0.5 mL) at 0 °C under Ar. After 15 min, the mixture was diluted with EtOAc and washed sequentially with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $Na_2SO_4$ and concentrated to get crude tris-TBS derivative. A

solution of aqueous LiOH (0.5 M; 0.15 mL, 0.075 mmol) was added to a solution of the above crude tris-TBS derivative in THF (0.4 mL) at 0 $^{o}$C. After 30 min the reaction mixture was diluted with $CH_2Cl_2$ and washed with 10% HCl. The organic layer was dried over $Na_2SO_4$, concentrated and fractionated by FCC (10% MeOH in $CH_2Cl_2$) to afford compound **422** (0.013 g, 90%) as an oil.

**[α]$_D$** −126 (*c* 0.40, $CH_3OH$)

**IR** $\nu_{max}$ 3153, 1732, 1630 cm$^{-1}$.

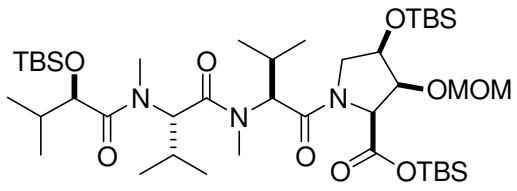
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.10 (1H, d, *J* = 11 Hz, Val$^2$-HC-2), 5.01 (1H, d, *J* = 11 Hz, Val$^1$-HC-2), 4.83 (1H, d, *J* = 7 Hz, $H_2CO_2$), 4.70 (1H, d, *J* = 7 Hz, $H_2CO_2$), 4.61 (1H, d, *J* = 7 Hz, Pro-HC-2), 4.41 (1H, dd, *J* = 4, 7 Hz, ProHC-3), 4.22-4.14 (2H, m, Pro-HC-4, HC-5 ), 4.10 (1H, d, *J* = 7 Hz, Hmb-HC-2), 3.70 (1H, ddd, *J* = 5, 9, 9 Hz, Pro-HC-5), 3.37 (3H, s, $H_3CO$), 3.19 (3H, s, Val$^1$-$H_3CN$), 3.13 (3H, s, Val$^2$-$H_3CN$), 2.36-2.24 (2H, m, Val$^1$-HC-3 ,Val$^2$-HC-3), 1.94 (1H, dqq, *J* = 7, 6.5, 6.5 Hz, Hmb-HC-3), 0.97 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.93 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.91 (9H, s, $(H_3C)_3C$), 0.89 (9H, s, $(H_3C)_3C$), 0.88 (3H, d, *J* = 6.5 Hz, Hmb-$H_3C$-4), 0.87 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.82 (3H, d, *J* = 6.5 Hz, Val$^2$-$H_3C$-4), 0.78 (3H, d, *J* = 6.5 Hz, Val$^1$-$H_3C$-4), 0.13 (3H, s, $H_3CSi$), 0.12 (3H, s, $H_3CSi$), 0.03 (3H, s, $H_3CSi$), 0.02 (3H, s, $H_3CSi$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.5 (s, Hmb-CO), 172.4 (s, Val$^2$-CO), 170.2 (s, Val$^1$-CO), 169.1 (s, Pro-CO), 96.6 (t, $CH_2O2$), 79.8 (d, Hmb-C-2), 74.6 (d, Pro-C-3), 72.7 (d, Pro-C-4 ), 61.3 (d, Pro-C-2), 58.8 (d, Val$^1$-C-2), 58.6 (d, Val$^2$-C-2), 56.4 (q, $CH_3O$), 51.7 (t, Pro-C-5), 32.0 (d, Hmb-C-3 ), 31.0 (q, Val$^1$-$CH_3N$), 30.2 (q, Val$^2$-$CH_3N$), 27.8 (d, Val$^2$-C-3 ), 27.7 (d, Val$^1$-C-3), 26.0 (q, $(CH_3)_3C$), 25.8 (q, $(CH_3)_3C$), 19.64 (q, Val$^2$-C-4), 19.58 (q, Val$^2$-C-4), 19.1 (q, Hmb-C-4), 19.0 (q, Val$^1$-C-4), 18.7 (q, Val$^1$-C-4), 18.4 (s, $C(CH_3)_3$), 18.3 (s, $C(CH_3)_3$), 18.2 (q, Hmb-C-4), -4.4 (q, $CH_3Si$), -4.8 (q, $CH_3Si$), -4.9 (q, $CH_3Si$), -5.0 (q, $CH_3Si$).

**LRMS** (ESI), *m/z* (relative intensity): 746 ([M+1]$^+$, 100), 441 (16), 328 (12).

**HRMS** *m/z* calcd for $C_{36}H_{71}N_3O_9Si_2$ 745.4729 (746.4801 for M+H), found 746.4825 (ESI).

**TBS-Hmb-MeVal-MeVal-(4-OTBS)(3-OMOM)Pro-OTBS**




**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.09 (1H, d, *J* = 11 Hz, $Val^2$-HC-2), 5.01 (1H, d, *J* = 11 Hz, $Val^1$-HC-2), 4.89 (1H, d, *J* = 6.5 Hz, $OCH_2O$), 4.68 (1H, d, *J* = 6.5 Hz, $OCH_2O$), 4.56 (1H, d, *J* = 6 Hz, Pro-HC-2), 4.39 (1H, dd, *J* = 6,6 Hz, Pro-HC-3), 4.37 (1H, dd, *J* = 6, 10 Hz, Pro-HC-5), 4.10 (1H, d, *J* = 6.5 Hz, Hmb-HC-2), 4.03 (1H, ddd, *J* = 4, 6, 10 Hz, Pro-HC-4), 3.56 (1H, dd, *J* = 10, 10 Hz, Pro-HC-5), 3.36 (3H, s, $H_3CO$), 3.19 (3H, s, $Val^2$-$H_3CN$), 3.14 (3H, s, $Val^1$-$H_3CN$), 2.22-2.36 (2H, m, $Val^1$-HC-3, $Val^2$-HC-3), 1.90-2.00 (1H, m, Hmb-HC-3), 1.01 (3H, d, *J* = 6.5 Hz), 0.93 (9H, s, $(H_3C)3C$), 0.91 (3H, d, *J* = 6.5 Hz), 0.90 (9H, s, $(H_3C)3C$), 0.89 (9H, s, $(H_3C)_3C$), 0.86 (3H, d, *J* = 6.5 Hz), 0.82 (3H, d, *J* = 6.5 Hz), 0.77 (3H, d, *J* = 6.5 Hz), 0.29 (3H, s, $H_3CSi$), 0.26 (3H, s, $H_3CSi$), 0.11 (3H, s, $H_3CSi$), 0.089 (3H, s, $H_3CSi$), 0.028 (3H, s, $H_3CSi$), 0.014 (3H, s, $H_3CSi$).

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